L Number	Hits	Search Text	DB	Time stamp
1	0	walterova?	USPAT; EPO; JPO; DERWENT	2001/11/02 14:27
2	0	walterova.in	USPAT; EPO; JPO; DERWENT	2001/11/02 14:27
3	0	walterova$.in	USPAT; EPO; JPO; DERWENT	2001/11/02 14:27
4	2	walterova$.in.	USPAT; EPO; JPO; DERWENT	2001/11/02 14:28
5	679	alkaloid same (isolat$4 or purif$ or extrac$) same (plant or herb or papaveraceae or cactacea or leguminoseae or fumariacea)	USPAT; EPO; JPO; DERWENT	2001/11/02 14:31
6	85	(alkaloid same (isolat$4 or purif$ or extrac$) same (plant or herb or papaveraceae or cactacea or leguminoseae or fumariacea)) same (chromat$ or column or hplc or waters!)	USPAT; EPO; JPO; DERWENT	2001/11/02 14:36
7	5	((alkaloid same (isolat$4 or purif$ or extrac$) same (plant or herb or papaveraceae or cactacea or leguminoseae or fumariacea)) same (chromat$ or column or hplc or waters!)) same (neutral$7)	USPAT; EPO; JPO; DERWENT	2001/11/02 14:47
8	0	huperzine same isoquinoline	USPAT; EPO; JPO; DERWENT	2001/11/02 14:47
9	4	huperzine and isoquinoline	USPAT; EPO; JPO; DERWENT	2001/11/02 14:47

$%^STN;HighlightOn= ***;HighlightOff=*** ;
Trying 3106016892...Open

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LOGINID:ssspta1651pxp
PASSWORD:
TERMINAL (ENTER 1, 2, 3, OR ?):2

* * * * * * * * * * Welcome to STN International * * * * * * * * * *

NEWS 1		Web Page URLs for STN Seminar Schedule - N. America
NEWS 2	Dec 17	The CA Lexicon available in the CAPLUS and CA files
NEWS 3	Feb 06	Engineering Information Encompass files have new names
NEWS 4	Feb 16	TOXLINE no longer being updated
NEWS 5	Apr 23	Search Derwent WPINDEX by chemical structure
NEWS 6	Apr 23	PRE-1967 REFERENCES NOW SEARCHABLE IN CAPLUS AND CA
NEWS 7	May 07	DGENE Reload
NEWS 8	Jun 20	Published patent applications (A1) are now in USPATFULL
NEWS 9	JUL 13	New SDI alert frequency now available in Derwent's DWPI and DPCI
NEWS 10	Aug 23	In-process records and more frequent updates now in MEDLINE
NEWS 11	Aug 23	PAGE IMAGES FOR 1947-1966 RECORDS IN CAPLUS AND CA
NEWS 12	Aug 23	Adis Newsletters (ADISNEWS) now available on STN
NEWS 13	Sep 17	IMSworld Pharmaceutical Company Directory name change to PHARMASEARCH
NEWS 14	Oct 09	Korean abstracts now included in Derwent World Patents Index
NEWS 15	Oct 09	Number of Derwent World Patents Index updates increased
NEWS 16	Oct 15	Calculated properties now in the REGISTRY/ZREGISTRY File
NEWS 17	Oct 22	Over 1 million reactions added to CASREACT
NEWS 18	Oct 22	DGENE GETSIM has been improved
NEWS 19	Oct 29	AAASD no longer available

NEWS EXPRESS	August 15 CURRENT WINDOWS VERSION IS V6.0c, CURRENT MACINTOSH VERSION IS V6.0 (ENG) AND V6.0J (JP), AND CURRENT DISCOVER FILE IS DATED 07 AUGUST 2001
NEWS HOURS	STN Operating Hours Plus Help Desk Availability
NEWS INTER	General Internet Information
NEWS LOGIN	Welcome Banner and News Items
NEWS PHONE	Direct Dial and Telecommunication Network Access to STN
NEWS WWW	CAS World Wide Web Site (general information)

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FILE 'HOME' ENTERED AT 11:15:07 ON 02 NOV 2001

=> index bioscience napralert

FILE 'DRUGMONOG' ACCESS NOT AUTHORIZED
COST IN U.S. DOLLARS                                    SINCE FILE      TOTAL
                                                           ENTRY    SESSION
FULL ESTIMATED COST                                         0.60       0.60

INDEX 'ADISALERTS, ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, AQUASCI,
       BIOBUSINESS, BIOCOMMERCE, BIOSIS, BIOTECHABS, BIOTECHDS, BIOTECHNO, CABA,
       CANCERLIT, CAPLUS, CEABA-VTB, CEN, CIN, CONFSCI, CROPB, CROPU, DDFB,
       DDFU, DGENE, DRUGB, DRUGLAUNCH, DRUGMONOG2, ...'
ENTERED AT 11:17:07 ON 02 NOV 2001

60 FILES IN THE FILE LIST IN STNINDEX

Enter SET DETAIL ON to see search term postings or to view
search error messages that display as 0* with SET DETAIL OFF.

=> s morphine(1) poppy (1) (extract? or isolat? or purif?)

          7   FILE AGRICOLA
         13   FILE ANABSTR
          1   FILE BIOBUSINESS
         35   FILE BIOSIS
         14   FILE BIOTECHABS
         14   FILE BIOTECHDS
          9   FILE BIOTECHNO
  12 FILES SEARCHED...
         19   FILE CABA
         93   FILE CAPLUS
         10   FILE CIN
          4   FILE DDFU
  23 FILES SEARCHED...
         25   FILE DGENE
          9   FILE DRUGU
         24   FILE EMBASE
          7   FILE ESBIOBASE
  34 FILES SEARCHED...
          1   FILE HEALSAFE
          3   FILE IFIPAT
          3   FILE JICST-EPLUS
          7   FILE LIFESCI
         25   FILE MEDLINE
  46 FILES SEARCHED...
          2   FILE NTIS
          4   FILE PASCAL
         19   FILE PHIN
         16   FILE PROMT
         16   FILE SCISEARCH
         17   FILE TOXLIT
         29   FILE USPATFULL
         14   FILE WPIDS
  58 FILES SEARCHED...
         14   FILE WPINDEX
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          7   FILE NAPRALERT

  30 FILES HAVE ONE OR MORE ANSWERS,   60 FILES SEARCHED IN STNINDEX

L1   QUE MORPHINE(L) POPPY (L) (EXTRACT? OR ISOLAT? OR PURIF?)

=> s l1 and (method? or proce? or protocol?)

          1   FILE AGRICOLA
          8   FILE ANABSTR
          1   FILE BIOBUSINESS
         18   FILE BIOSIS
   9 FILES SEARCHED...
          3   FILE BIOTECHABS
          3   FILE BIOTECHDS
          3   FILE BIOTECHNO
          9   FILE CABA
         46   FILE CAPLUS
  15 FILES SEARCHED...
          1   FILE CIN
          3   FILE DDFU
         10   FILE DGENE
  24 FILES SEARCHED...
          6   FILE DRUGU
         14   FILE EMBASE
          2   FILE ESBIOBASE
  33 FILES SEARCHED...
          3   FILE IFIPAT
  40 FILES SEARCHED...
          3   FILE JICST-EPLUS
          2   FILE LIFESCI
         10   FILE MEDLINE
          2   FILE NTIS
  47 FILES SEARCHED...
          3   FILE PASCAL
  49 FILES SEARCHED...
          1   FILE PHIN
          9   FILE PROMT
          3   FILE SCISEARCH
          7   FILE TOXLIT
         29   FILE USPATFULL
  57 FILES SEARCHED...
          9   FILE WPIDS
          9   FILE WPINDEX
  59 FILES SEARCHED...
          4   FILE NAPRALERT

  29 FILES HAVE ONE OR MORE ANSWERS,   60 FILES SEARCHED IN STNINDEX

L2   QUE L1 AND (METHOD? OR PROCE? OR PROTOCOL?)

=> 2 and vat extract?
<------User Break------>
u
=> s l2 and vat extract?

   9 FILES SEARCHED...
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  14 FILES SEARCHED...
  23 FILES SEARCHED...
  33 FILES SEARCHED...
<------User Break------>
u
=> s l1 and vat extract?

  14 FILES SEARCHED...
<------User Break------>
u
=> s isoquinoline alkaloid or codeine or curare or heroin or morphine or
papaverine or tubocurarine or benzylisoquinoline alkaloid?

       4072   FILE ADISALERTS
        173   FILE ADISINSIGHT
        850   FILE ADISNEWS
        561   FILE AGRICOLA
       1368   FILE ANABSTR
        171   FILE AQUASCI
        743   FILE BIOBUSINESS
         55   FILE BIOCOMMERCE
      57504   FILE BIOSIS
        238   FILE BIOTECHABS
        238   FILE BIOTECHDS
       3295   FILE BIOTECHNO
       1764   FILE CABA
       3086   FILE CANCERLIT
      47508   FILE CAPLUS
         52   FILE CEABA-VTB
         47   FILE CEN
        648   FILE CIN
       1926   FILE CONFSCI
         20   FILE CROPB
         32   FILE CROPU
  21 FILES SEARCHED...
      20623   FILE DDFB
      29875   FILE DDFU
       1843   FILE DGENE
      20623   FILE DRUGB
        978   FILE DRUGLAUNCH
       4719   FILE DRUGMONOG2
        104   FILE DRUGNL
      31743   FILE DRUGU
        119   FILE DRUGUPDATES
        273   FILE EMBAL
      73230   FILE EMBASE
       6227   FILE ESBIOBASE
         21   FILE FROSTI
         22   FILE FSTA
        115   FILE GENBANK
        248   FILE HEALSAFE
  39 FILES SEARCHED...
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       3680   FILE JICST-EPLUS
          7   FILE KOSMET
       8111   FILE LIFESCI
         16   FILE MEDICONF
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     53931   FILE MEDLINE
       437   FILE NIOSHTIC
       617   FILE NTIS
        26   FILE OCEAN
     15458   FILE PASCAL
       247   FILE PHAR
        12   FILE PHIC
      1316   FILE PHIN
      3512   FILE PROMT
     35286   FILE SCISEARCH
  54 FILES SEARCHED...
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     30119   FILE TOXLIT
      7020   FILE USPATFULL
      2471   FILE WPIDS
      2471   FILE WPINDEX
      8862   FILE NAPRALERT

  58 FILES HAVE ONE OR MORE ANSWERS,   60 FILES SEARCHED IN STNINDEX

L3   QUE ISOQUINOLINE ALKALOID OR CODEINE OR CURARE OR HEROIN OR MORPHINE OR PA
       PAVERINE OR TUBOCURARINE OR BENZYLISOQUINOLINE ALKALOID?

=> s l3 (l) (extract? or purif? or isolat?)

        80   FILE ADISALERTS
        19   FILE ADISINSIGHT
        19   FILE ADISNEWS
        68   FILE AGRICOLA
       431   FILE ANABSTR
        41   FILE AQUASCI
        73   FILE BIOBUSINESS
         1   FILE BIOCOMMERCE
      3449   FILE BIOSIS
       123   FILE BIOTECHABS
       123   FILE BIOTECHDS
       442   FILE BIOTECHNO
  12 FILES SEARCHED...
       337   FILE CABA
       107   FILE CANCERLIT
      5065   FILE CAPLUS
        10   FILE CEABA-VTB
        16   FILE CEN
        48   FILE CIN
        38   FILE CONFSCI
         5   FILE CROPU
       302   FILE DDFB
      1570   FILE DDFU
       176   FILE DGENE
       302   FILE DRUGB
        26   FILE DRUGLAUNCH
       385   FILE DRUGMONOG2
  27 FILES SEARCHED...
         1   FILE DRUGNL
      2888   FILE DRUGU
        12   FILE DRUGUPDATES
        20   FILE EMBAL
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      3354   FILE EMBASE
       684   FILE ESBIOBASE
         2   FILE FROSTI
         5   FILE FSTA
        10   FILE GENBANK
         8   FILE HEALSAFE
        66   FILE IFIPAT
  40 FILES SEARCHED...
       198   FILE JICST-EPLUS
       674   FILE LIFESCI
      3188   FILE MEDLINE
        56   FILE NIOSHTIC
        49   FILE NTIS
         7   FILE OCEAN
       873   FILE PASCAL
        22   FILE PHAR
       111   FILE PHIN
       194   FILE PROMT
      1700   FILE SCISEARCH
  54 FILES SEARCHED...
         1   FILE SYNTHLINE
      2965   FILE TOXLIT
      4516   FILE USPATFULL
       241   FILE WPIDS
       241   FILE WPINDEX
      4938   FILE NAPRALERT

  54 FILES HAVE ONE OR MORE ANSWERS,   60 FILES SEARCHED IN STNINDEX

L4   QUE L3 (L) (EXTRACT? OR PURIF? OR ISOLAT?)

=> s l4 and vat extract?
<------User Break------>
u
=> s l4 and vat

  13 FILES SEARCHED...
  23 FILES SEARCHED...
  37 FILES SEARCHED...
  49 FILES SEARCHED...
         1   FILE SCISEARCH
        18   FILE USPATFULL
         1   FILE WPIDS
  58 FILES SEARCHED...
         1   FILE WPINDEX

   4 FILES HAVE ONE OR MORE ANSWERS,   60 FILES SEARCHED IN STNINDEX

L5   QUE L4 AND VAT

=> d rank

F1          18   USPATFULL
F2           1   SCISEARCH
F3           1   WPIDS
F4           1   WPINDEX
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=> fil f2

COST IN U.S. DOLLARS                                    SINCE FILE      TOTAL
                                                           ENTRY    SESSION
FULL ESTIMATED COST                                        14.85      15.45

FILE 'SCISEARCH' ENTERED AT 11:36:54 ON 02 NOV 2001
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FILE COVERS 1974 TO 26 Oct 2001 (20011026/ED)

=> s l5

          2535 ISOQUINOLINE
          9643 ALKALOID
           117 ISOQUINOLINE ALKALOID
                 (ISOQUINOLINE(W)ALKALOID)
          2000 CODEINE
           457 CURARE
          4229 HEROIN
         26191 MORPHINE
          2433 PAPAVERINE
          1478 TUBOCURARINE
           196 BENZYLISOQUINOLINE
         25042 ALKALOID?
           128 BENZYLISOQUINOLINE ALKALOID?
                 (BENZYLISOQUINOLINE(W)ALKALOID?)
        257688 EXTRACT?
        200469 PURIF?
        488986 ISOLAT?
          1700 L3 (L) (EXTRACT? OR PURIF? OR ISOLAT?)
           811 VAT
L6           1 L4 AND VAT

=> d l6 1- all

YOU HAVE REQUESTED DATA FROM 1 ANSWERS - CONTINUE? Y/(N):y


L6   ANSWER 1 OF 1  SCISEARCH  COPYRIGHT 2001 ISI (R)
AN   95:779834  SCISEARCH
GA   The Genuine Article (R) Number: TD066
TI   MORPHINE-INDUCED ALTERATIONS ON DNA-BINDING PROTEINS IN DEVELOPING
     RAT-BRAIN
AU   TENCHEVA Z (Reprint); VELICHKOVA A; ANGELOVA A
CS   BULGARIAN ACAD SCI, BRAIN RES INST, ACAD G BONCHEV B123, BU-1113 SOFIA,
     BULGARIA (Reprint); UNIV SOFIA, DEPT BIOCHEM, SOFIA, BULGARIA
CYA  BULGARIA
SO   METHODS AND FINDINGS IN EXPERIMENTAL AND CLINICAL PHARMACOLOGY, (SEP 1995)
     Vol. 17, No. 7, pp. 449-454.
     ISSN: 0379-0355.
DT   Article; Journal
FS   LIFE
LA   ENGLISH
REC  Reference Count: 22
AB       Endogenous opioids and opiate drugs inhibit nervous system maturation
```

through both direct and indirect mechanisms. Recently much attention has been directed toward changes in the postreceptor events and it has been speculated that the regulation of gene expression may be involved in the development of drug tolerance and dependence. We investigated the changes in the levels of in vitro RNA synthesis in developing rat brain after continuous block of opioid receptors. Repeated naloxone treatment induced increased levels (27-48%) of RNA synthesis during the early postnatal period. Using mobility gel shift assay the presence of octamer binding proteins (Oct-1) and the replication differentiation transcription factor CTF/NF1 in the developing ***vat*** brain were studied both after single or repeated ***morphine*** and naloxone treatment. Decreased Oct-1 binding activity in brain protein ***extracts*** 1 h after ***morphine*** application was registered, while opioid antagonist naloxone exerted an opposite effect on this octamer protein following single drug treatment. Repeated administration of ***morphine*** or naloxone decreased markedly the DNA-binding affinity of Oct-1. The binding activity of CTF/NF1 changes differently showed higher levels assessed 30-120 min after ***morphine*** administration. The opposite trend of the changes in opiate drug and opioid antagonist animals suggests opioid receptor-mediated regulation of Oct-1 and CTF/NF1 transcription factors.

CC PHARMACOLOGY & PHARMACY

ST Author Keywords: MORPHINE; NALOXONE; DNA BINDING PROTEINS; OCT-1; CTF/NF1; TRANSCRIPTIONAL REGULATION; TRANSCRIPTION FACTORS; DEVELOPING BRAIN

STP KeyWords Plus (R): CELL-PROLIFERATION; MAMMALIAN-CELLS; TRANSCRIPTION; REPLICATION; ANTAGONIST; NALTREXONE; EXPOSURE; NALOXONE; REGIONS

RF 93-3472 002; RNA POLYMERASE-II TRANSCRIPTION; TATA-BINDING PROTEIN; ACTIVATION DOMAINS; FUNCTIONAL PREINITIATION COMPLEX
93-6382 001; PIT-1/GHF-1 TRANSCRIPTION FACTOR EXPRESSION; POU DOMAIN PROTEIN; RAT THYROTROPIN-BETA GENE

RE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)
ANDREWS N C	1991	19	2499	NUCLEIC ACIDS RES
BARDO M T	1983	22	453	NEUROPHARMACOLOGY
CHANG S L	1993	4	25	MOL CELL NEUROSCI
COYLE J T	1976	15	555	NEUROPHARMACOLOGY
HADJIOLOV A A	1965	26	383	J CELL BIOL
HAUSER K F	1993		23	NEUROBIOLOGY OPIATES
HE X	1989	340	35	NATURE
JOHNSON P F	1989	58	799	ANNU REV BIOCHEM
KORNBLUM H I	1987	31	45	DEV BRAIN RES
LORBER B A	1990	531	329	BRAIN RES
MASEDA C	1983	14	S 237	NEUROSCI LETT S
MITCHELL P J	1989	245	371	SCIENCE
OSUGI T	1994	21	256	MOL BRAIN RES
SANTORO C	1988	334	218	NATURE
SCHMAHL W	1989	486	297	BRAIN RES
SCHREIBER E	1989		33	TISSUE SPECIFIC GENE
SOLLNERWEBB B	1975	14	2915	BIOCHEMISTRY-US
TSANG D	1980	188	199	BRAIN RES
TSANG D	1982	3	637	DEV BRAIN RES

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INDEX 'ADISALERTS, ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, AQUASCI, BIOBUSINESS, BIOCOMMERCE, BIOSIS, BIOTECHABS, BIOTECHDS, BIOTECHNO, CABA, CANCERLIT, CAPLUS, CEABA-VTB, CEN, CIN, CONFSCI, CROPB, CROPU, DDFB, DDFU, DGENE, DRUGB, DRUGLAUNCH, DRUGMONOG2, ...' ENTERED AT 11:17:07 ON 02 NOV 2001

SEA MORPHINE(L) POPPY (L) (EXTRACT? OR ISOLAT? OR PURIF?)

7	FILE AGRICOLA
13	FILE ANABSTR
1	FILE BIOBUSINESS
35	FILE BIOSIS
14	FILE BIOTECHABS
14	FILE BIOTECHDS
9	FILE BIOTECHNO
19	FILE CABA
93	FILE CAPLUS
10	FILE CIN
4	FILE DDFU
25	FILE DGENE
9	FILE DRUGU
24	FILE EMBASE
7	FILE ESBIOBASE
1	FILE HEALSAFE
3	FILE IFIPAT
3	FILE JICST-EPLUS
7	FILE LIFESCI
25	FILE MEDLINE
2	FILE NTIS
4	FILE PASCAL
19	FILE PHIN
16	FILE PROMT
16	FILE SCISEARCH
17	FILE TOXLIT
29	FILE USPATFULL
14	FILE WPIDS
14	FILE WPINDEX
7	FILE NAPRALERT

L1 QUE MORPHINE(L) POPPY (L) (EXTRACT? OR ISOLAT? OR PURIF?)

SEA L1 AND (METHOD? OR PROCE? OR PROTOCOL?)

1	FILE AGRICOLA
8	FILE ANABSTR
1	FILE BIOBUSINESS
18	FILE BIOSIS
3	FILE BIOTECHABS
3	FILE BIOTECHDS
3	FILE BIOTECHNO
9	FILE CABA
46	FILE CAPLUS
1	FILE CIN
3	FILE DDFU
10	FILE DGENE
6	FILE DRUGU

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            14   FILE EMBASE
             2   FILE ESBIOBASE
             3   FILE IFIPAT
             3   FILE JICST-EPLUS
             2   FILE LIFESCI
            10   FILE MEDLINE
             2   FILE NTIS
             3   FILE PASCAL
             1   FILE PHIN
             9   FILE PROMT
             3   FILE SCISEARCH
             7   FILE TOXLIT
            29   FILE USPATFULL
             9   FILE WPIDS
             9   FILE WPINDEX
             4   FILE NAPRALERT
L2            QUE L1 AND (METHOD? OR PROCE? OR PROTOCOL?)
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              SEA 2 AND VAT EXTRACT?
              ---------
              SEA L2 AND VAT EXTRACT?
              ---------
              SEA L1 AND VAT EXTRACT?
              ---------
              SEA ISOQUINOLINE ALKALOID OR CODEINE OR CURARE OR HEROIN OR MOR
              ---------
          4072   FILE ADISALERTS
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           850   FILE ADISNEWS
           561   FILE AGRICOLA
          1368   FILE ANABSTR
           171   FILE AQUASCI
           743   FILE BIOBUSINESS
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         57504   FILE BIOSIS
           238   FILE BIOTECHABS
           238   FILE BIOTECHDS
          3295   FILE BIOTECHNO
          1764   FILE CABA
          3086   FILE CANCERLIT
         47508   FILE CAPLUS
            52   FILE CEABA-VTB
            47   FILE CEN
           648   FILE CIN
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            20   FILE CROPB
            32   FILE CROPU
         20623   FILE DDFB
         29875   FILE DDFU
          1843   FILE DGENE
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           978   FILE DRUGLAUNCH
          4719   FILE DRUGMONOG2
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         31743   FILE DRUGU
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           273   FILE EMBAL
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  3680   FILE JICST-EPLUS
     7   FILE KOSMET
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    16   FILE MEDICONF
 53931   FILE MEDLINE
   437   FILE NIOSHTIC
   617   FILE NTIS
    26   FILE OCEAN
 15458   FILE PASCAL
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    12   FILE PHIC
  1316   FILE PHIN
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  8862   FILE NAPRALERT
L3          QUE ISOQUINOLINE ALKALOID OR CODEINE OR CURARE OR HEROIN OR MOR
            ---------
            SEA L3 (L) (EXTRACT? OR PURIF? OR ISOLAT?)
            ---------
    80   FILE ADISALERTS
    19   FILE ADISINSIGHT
    19   FILE ADISNEWS
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    41   FILE AQUASCI
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    10   FILE CEABA-VTB
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     5   FILE CROPU
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    26   FILE DRUGLAUNCH
   385   FILE DRUGMONOG2
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              1   FILE DRUGNL
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             20   FILE EMBAL
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              5   FILE FSTA
             10   FILE GENBANK
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             56   FILE NIOSHTIC
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              7   FILE OCEAN
            873   FILE PASCAL
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           1700   FILE SCISEARCH
              1   FILE SYNTHLINE
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           4516   FILE USPATFULL
            241   FILE WPIDS
            241   FILE WPINDEX
           4938   FILE NAPRALERT
L4             QUE L3 (L) (EXTRACT? OR PURIF? OR ISOLAT?)
               ---------
               SEA L4 AND VAT EXTRACT?
               ---------
               SEA L4 AND VAT
               ---------
               1   FILE SCISEARCH
              18   FILE USPATFULL
               1   FILE WPIDS
               1   FILE WPINDEX
L5             QUE L4 AND VAT
               ---------

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L6             1 S L5

=> index bioscience

FILE 'DRUGMONOG' ACCESS NOT AUTHORIZED
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                         ENTRY    SESSION
FULL ESTIMATED COST                                       5.94      21.39

INDEX 'ADISALERTS, ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, AQUASCI,
       BIOBUSINESS, BIOCOMMERCE, BIOSIS, BIOTECHABS, BIOTECHDS, BIOTECHNO, CABA,
       CANCERLIT, CAPLUS, CEABA-VTB, CEN, CIN, CONFSCI, CROPB, CROPU, DDFB,
       DDFU, DGENE, DRUGB, DRUGLAUNCH, DRUGMONOG2, ...'
ENTERED AT 11:38:17 ON 02 NOV 2001
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59 FILES IN THE FILE LIST IN STNINDEX

Enter SET DETAIL ON to see search term postings or to view
search error messages that display as 0* with SET DETAIL OFF.

=> s l4 (l) acid (l) neutraliz?

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          4   FILE ANABSTR
          5   FILE BIOSIS
          2   FILE BIOTECHNO
  12 FILES SEARCHED...
         24   FILE CAPLUS
  19 FILES SEARCHED...
          5   FILE DRUGU
  29 FILES SEARCHED...
          6   FILE EMBASE
          1   FILE ESBIOBASE
          4   FILE IFIPAT
  40 FILES SEARCHED...
          1   FILE LIFESCI
          5   FILE MEDLINE
          1   FILE PASCAL
  49 FILES SEARCHED...
          2   FILE PROMT
          4   FILE SCISEARCH
          1   FILE SYNTHLINE
          1   FILE TOXLIT
        870   FILE USPATFULL
  58 FILES SEARCHED...

  16 FILES HAVE ONE OR MORE ANSWERS,   59 FILES SEARCHED IN STNINDEX
```

L7 QUE L4 (L) ACID (L) NEUTRALIZ?

=> s l7 and (column? or chromatog? or hplc)

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          3   FILE ANABSTR
          3   FILE BIOSIS
  11 FILES SEARCHED...
          2   FILE BIOTECHNO
          9   FILE CAPLUS
  17 FILES SEARCHED...
          1   FILE DRUGU
  29 FILES SEARCHED...
          4   FILE EMBASE
  38 FILES SEARCHED...
          1   FILE LIFESCI
          3   FILE MEDLINE
          1   FILE PASCAL
  49 FILES SEARCHED...
          3   FILE SCISEARCH
        763   FILE USPATFULL
  58 FILES SEARCHED...

  11 FILES HAVE ONE OR MORE ANSWERS,   59 FILES SEARCHED IN STNINDEX
```

L8 QUE L7 AND (COLUMN? OR CHROMATOG? OR HPLC)

=> d rank

F1	763	USPATFULL
F2	9	CAPLUS
F3	4	EMBASE
F4	3	ANABSTR
F5	3	BIOSIS
F6	3	MEDLINE
F7	3	SCISEARCH
F8	2	BIOTECHNO
F9	1	DRUGU
F10	1	LIFESCI
F11	1	PASCAL

=> fil f2, f5, f6, f7, f10

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	4.05	25.44

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=> s l8

L9 19 L8

=> dup rem l9\

ENTER L# LIST OR (END):end

=> dup rem l9

PROCESSING COMPLETED FOR L9
L10 13 DUP REM L9 (6 DUPLICATES REMOVED)

=> d l10 1- all

YOU HAVE REQUESTED DATA FROM 13 ANSWERS - CONTINUE? Y/(N):y

L10 ANSWER 1 OF 13 BIOSIS COPYRIGHT 2001 BIOSIS DUPLICATE 1
AN 1995:71955 BIOSIS
DN PREV199598086255
TI Hair analysis for buprenorphine and its dealkylated metabolite by RIA and confirmation by LC/ECD.
AU Kintz, Pascal (1); Cirimele, Vincent; Edel, Yves; Jamey, Carole; Mangin, Patrice
CS (1) Inst. Med. Legale, 11 rue Humann, 67000 Strasbourg France
SO Journal of Forensic Sciences, (1994) Vol. 39, No. 6, pp. 1497-1503. ISSN: 0022-1198.
DT Article
LA English
AB Hair samples were obtained from 14 subjects admitted 2 or 3 months previously to a detoxification center. All reported an history of intravenous ***heroin*** abuse. After decontamination by two dichloromethane washes, about 50 mg hair were pulverized in a ball mill and incubated at 56 degree C overnight in 1 mL 0.1 HCl. After ***neutralization*** , buprenorphine analyzed by RIA was in the range of 0.01 to 0.47 ng/mg. To confirm buprenorphine, liquid ***chromatography*** was used. After ***neutralization*** , drugs were ***extracted*** with toluene at pH 8.5 during a 3-step ***extraction*** procedure. A portion of the reconstituted residue was injected into a Lichrosorb CN ***column*** , with a mobile phase of phosphate buffer (pH 4.0)-acetonitrile-1-heptane sulfonic ***acid*** -butylamine (85:17:2:0.01, v/v). Detection was achieved by coulometry, and the potential of the electrodes was 0.15 and 0.50 V, respectively. Linear calibration curves were obtained from 0.02 to 2.0 ng/mg with a correlation coefficient r gt 0.99 for both drugs. The detection limit for the major metabolite was about 0.01 ng/mg and 0.02 ng/mg for buprenorphine, using a 50 mg hair sample. Recovery (at 0.2 ng/mg) was 54 and 62% for norbuprenorphine and buprenorphine, respectively. Drugs concentrations in hair were in the range 0.02-0.59 and not detected-0.15 ng/mg for buprenorphine and norbuprenorphine, respectively. Results suggest that a dose-response relationship exists between the concentration of buprenorphine in hair and the administered dose.
CC General Biology - Forensic Science *00531
Radiation - Radiation and Isotope Techniques *06504
Behavioral Biology - Human Behavior *07004
Biochemical Methods - General *10050
Biochemical Studies - General *10060
Psychiatry - Addiction - Alcohol, Drugs, Smoking, etc. *21004
Pharmacology - Drug Metabolism; Metabolic Stimulators *22003
Pharmacology - Clinical Pharmacology *22005
Pharmacology - Neuropharmacology *22024
Toxicology - Pharmacological Toxicology *22504
Immunology and Immunochemistry - General; Methods *34502
BC Hominidae *86215
IT Major Concepts
Behavior; Biochemistry and Molecular Biophysics; Forensics; Immune System (Chemical Coordination and Homeostasis); Methods and Techniques; Pharmacology; Psychiatry (Human Medicine, Medical Sciences); Radiology (Medical Sciences); Toxicology
IT Chemicals & Biochemicals
BUPRENORPHINE
IT Miscellaneous Descriptors
ANALYTICAL METHOD; DOSE-RESPONSE RELATIONSHIP; FORENSICS; HUMAN DRUG ABUSE; LIQUID ***CHROMATOGRAPHY*** /ELECTRON CAPTURE DETECTOR;

NARCOTICS; RADIOIMMUNOASSAY; TOXICOLOGY
ORGN Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
Hominidae (Hominidae)
ORGN Organism Superterms
animals; chordates; humans; mammals; primates; vertebrates
RN 52485-79-7 (BUPRENORPHINE)

L10 ANSWER 2 OF 13 BIOSIS COPYRIGHT 2001 BIOSIS DUPLICATE 2
AN 1993:372875 BIOSIS
DN PREV199396058550
TI Opiate concentrations in human head, axillary, and pubic hair.
AU Kintz, Pascal (1); Mangin, Patrice
CS (1) Inst. Med. Legale, 11 rue Humann, 67000 Strasbourg France
SO Journal of Forensic Sciences, (1993) Vol. 38, No. 3, pp. 657-662.
ISSN: 0022-1198.
DT Article
LA English
AB The concentrations of ***morphine*** and ***codeine*** were investigated in hair from the head, axillary and pubic regions obtained from 12 fatal ***heroin*** cases. Hair preparation involves a decontamination procedure in dichloromethane at 37 degree C for 15 min, solubilization in sodium hydroxyde at 100 degree C for 5 min, ***neutralization*** with hydrochloric ***acid*** and centrifugation. After ***extraction*** in chloroform-isopropanol-n-heptane (50:17:33; v/v) at pH 9.2, drugs were derivatized with BSTFA + 1% TMCS and separated on a 12-m BP-5 capillary ***column*** . Quantification was done by GC/MS using selected ion monitoring. The highest ***morphine*** concentrations were found in pubic hair (0.80 to 41.34 ng/mg), followed by hair of the head (0.62 to 27.10 ng/mg), and axillary hair (0.40 to 24.20 ng/mg). ***Codeine*** was also detected in all samples, and the ***codeine*** -to- ***morphine*** ratios ranged from 0.069 to 0.273. The differences observed in drug concentrations in the 3 types of hair are discussed in the light of the existing literature.
CC General Biology - Forensic Science *00531
Behavioral Biology - Human Behavior 07004
Clinical Biochemistry; General Methods and Applications *10006
Biochemical Studies - General 10060
Chordate Body Regions - Head *11304
Pathology, General and Miscellaneous - Diagnostic *12504
Reproductive System - Physiology and Biochemistry 16504
Integumentary System - Physiology and Biochemistry *18504
Psychiatry - Addiction - Alcohol, Drugs, Smoking, etc. *21004
Pharmacology - General *22002
Pharmacology - Drug Metabolism; Metabolic Stimulators *22003
Pharmacology - Neuropharmacology *22024
Pharmacology - Psychopharmacology *22026
Toxicology - Pharmacological Toxicology *22504
BC Hominidae *86215
IT Major Concepts
Clinical Chemistry (Allied Medical Sciences); Forensics; Integumentary System (Chemical Coordination and Homeostasis); Morphology; Pathology; Pharmacology; Psychiatry (Human Medicine, Medical Sciences); Toxicology
IT Chemicals & Biochemicals
CODEINE; MORPHINE

IT Miscellaneous Descriptors
ANALYTICAL METHOD; FORENSIC TOXICOLOGY; PHARMACOKINETICS
ORGN Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
human (Hominidae)
ORGN Organism Superterms
animals; chordates; humans; mammals; primates; vertebrates
RN 76-57-3 (CODEINE)
57-27-2 (MORPHINE)

L10 ANSWER 3 OF 13 BIOSIS COPYRIGHT 2001 BIOSIS DUPLICATE 3
AN 1994:211480 BIOSIS
DN PREV199497224480
TI Variability of opiates concentrations in human hair according to their anatomical origin: Head, axillary and pubic regions.
AU Mangin, Patrice (1); Kintz, Pascal
CS (1) Inst. de Med. Legale, 11 rue Humann, 67000 Strasbourg France
SO Forensic Science International, (1993) Vol. 63, No. 1-3, pp. 77-83. ISSN: 0379-0738.
DT Article
LA English
AB The concentrations of ***morphine*** and ***codeine*** were investigated in hair from the head. axillary and pubic regions obtained from 20 fatal ***heroin*** cases. Hair preparation involves decontamination procedure in dichloromethane at 37 degree C for 15 min, solubilization in sodium hydroxide at 100 degree C for 5 min, ***neutralization*** with hydrochloric ***acid*** and centrifugation. After ***extraction*** in chloroform/isopropanol/n-heptane (50:17:33; v/v) at pH 9.2, drugs were derivatized with BSTFA + 1% TMCS and separated on a 12-m BP-5 capillary ***column*** . Quantification was done by GC/MS using selected ion monitoring. The highest ***morphine*** concentrations were found in pubic hair (0.80-41.34 ng/mg), followed by hair of the head (0.62-27.10 ng/mg), and axillary hair (0.40-24.20 ng/mg). ***Codeine*** was also detected in all samples, and the ***codeine*** / ***morphine*** ratios ranged from 0.054 to 0.273. The differences observed in drug concentration in the three kinds of hair are discussed in the light of the existing literature.
CC Biochemical Studies - General 10060
Chordate Body Regions - Head *11304
Chordate Body Regions - Pelvis *11316
Metabolism - General Metabolism; Metabolic Pathways *13002
Integumentary System - Anatomy *18502
Integumentary System - Physiology and Biochemistry *18504
Psychiatry - Addiction - Alcohol, Drugs, Smoking, etc. *21004
BC Hominidae *86215
IT Major Concepts
Integumentary System (Chemical Coordination and Homeostasis); Metabolism; Morphology; Psychiatry (Human Medicine, Medical Sciences)
IT Chemicals & Biochemicals
MORPHINE; CODEINE
IT Miscellaneous Descriptors
CODEINE; MORPHINE
ORGN Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
Hominidae (Hominidae)

ORGN Organism Superterms
animals; chordates; humans; mammals; primates; vertebrates
RN 57-27-2 (MORPHINE)
76-57-3 (CODEINE)

L10 ANSWER 4 OF 13 LIFESCI COPYRIGHT 2001 CSA
AN 94:54322 LIFESCI
TI Variability of opiates concentrations in human hair according to their anatomical origin: Head, axillary and public regions
AU Mangin, P.; Kintz, P.
CS Inst. Med. Legale, 11 rue Humann, 67000 Strasbourg, France
SO FORENSIC SCI. INT., (1993) pp. 77-83.
Meeting Info.: 1. International Meeting on Hair Analysis as a Diagnostic Tool for Drugs of Abuse. Genoa (Italy). 10-11 Dec 1992.
ISSN: 0379-0738.
DT Book
TC Conference
FS X
LA English
SL English
AB The concentrations of ***morphine*** and ***codeine*** were investigated in hair from the head, axillary and pubic region obtained from 20 fatal ***heroin*** cases. Hair preparation involves decontamination procedure in dichloromethane at 37 degree C for 15 min, solubilization in sodium hydroxide at 100 degree C for 5 min, ***neutralization*** with hydrochloric ***acid*** and centrifugation. After ***extraction*** in chloroform/isopropanol/n-heptane (50:17:33; v/v) at pH 9.2, drugs were derivatized with BSTFA + 1% TMCS and separated on a 12-m BP-5 capillary ***column*** . Quantification was done by GC/S using selected ion monitoring. The highest ***morphine*** concentrations were found in pubic hair (0.80-41.34 ng/mg), followed by hair of the head (0.62-27.10 ng/mg), and axillary hair (0.40-24.20 ng/mg). ***Codeine*** was also detected in all samples, and the ***codeine*** / ***morphine*** ratios ranged from 0.054 to 0.273. The differences observed in drug concentration in the three kinds of hair are discussed in the light of the existing literature.
CC 24222 Analytical procedures; 24180 Social poisons & drug abuse; 24114 Metabolism
UT opiates; concentration; variation; hair; man; morphine; codeine

L10 ANSWER 5 OF 13 CAPLUS COPYRIGHT 2001 ACS
AN 1966:103109 CAPLUS
DN 64:103109
OREF 64:19317a-e
TI Ring opening of opium alkaloids by ion exchange
AU Buechi, J.; Moos, R. von
CS Eidg. Tech. Hochsch, Zurich, Switz.
SO Pharm. Acta Helv. (1966), 41(3), 142-63
DT Journal
LA German
CC 30 (Pharmaceuticals)
AB A review of the most important methods for the sepn. of the alkaloids is presented. Studies are concerned with the prepn. of the alkaloids and of the opium samples, choice and characteristics of ion-exchangers including pH values, speed of exchange, exchange equil., elution expts. with single alkaloids and with mixts. using Duolite C-25, Duolite C-10, Duolite CS 101, CAM L-124. The opium was extd. by ***column***

chromatography using Al2O3 and HCl. The alkaloids were sepd. by using 50 ml. of the ***acid*** ***purified*** opium ext. (= 0.5 g. opium), mixing with 2 g. Duolite C-10(NH4 form), and ***neutralizing*** by the addn. of some drops of concd. ammonia. After shaking for 5 min., the resin with adsorbed alkaloids was washed with 200 ml. H2O at 50.degree. and then filtered. Duolite C-10(NH4-form) (5 g.) was allowed to soak in an eluting soln. of 100:60 MeOH-H2O and placed in a ***chromatographic*** tube. After 30 min., elution with slight pos. pressure was conducted at the rate of 1 ml./min. Using MeOH-methylene chloride-buffer soln. pH 7 (100:50:60), 300 ml. contg. narcotine, ***papaverine*** , and narceine were obtained. Then using an eluant of MeOH-methylene chloride-2N NH4OH (100:50:60), 300 ml. eluate contg. ***morphine*** , ***codeine*** , thebaine, and crytopine was collected. Narceine was sepd. from narcotine and ***papaverine*** by using Duolite CS 101 (NH4 form); narceine eluted with MeOHH2O (15:85) and papavarine and narcotine with MeOH-methylene chloride-2N NH4OH (100:50:2). Narcotine was sepd. from ***papaverine*** by hydrolyzing the lactone ring of narcotine and sepg. the resulting .gamma.-hydroxy carboxylic ***acid*** from ***papaverine*** . Sepn. of ***morphine*** from thebaine and ***codeine*** was accomplished on Dowex (OH form); MeOH removed thebaine and ***codeine*** and 50% AcOH removed ***morphine*** . For the quant. detn. of the opium alkaloids after their sepn., the eluate is evapd. to dryness on a steam bath and the residue taken up with 10 ml. 2N AcOH and 10 ml. freshly prepd. satd. reineckate soln. is added; after standing for 60 min. the ppt. is filtered off by suction and washed with ice H2O. The reineckate is dissolved in a min. amt. of acetone, transferred to a 25-ml. flask, 2 ml. alk. Fehling no. 2 soln. and 40 ml. H2O are added followed by boiling for 10 min. To the cold soln. is added 20 ml. 25% HNO3 and 10 ml. 0.1N AgNO3; the excess AgNO3 is backtitrated with 0.1N NH4CNS soln. and the endpoint detd. electrometrically. The results obtained compare favorably with other methods and is preferred to the method of Anneler (CA 14, 3499). 49 references.

L10 ANSWER 6 OF 13 CAPLUS COPYRIGHT 2001 ACS
AN 1960:28745 CAPLUS
DN 54:28745
OREF 54:5654c-i,5655a-h
TI Synthesis of isoquinoline derivatives
AU Tachikawa, Ryuji
CS Univ. Tokyo
SO Tetrahedron (1959), 7, 118-22
DT Journal
LA Unavailable
CC 10G (Organic Chemistry: Heterocyclic Compounds)
GI For diagram(s), see printed CA Issue.
AB The Bischler-Napieralskir eaction was applied to the synthesis of several ***papaverine*** derivs. (I, R = R1,R2 = OMe, n = 1; R = Me, R1 = H, R2R2 = O2CH2, n = 1; R =Me, R1 = H,R2R2 = O2CH2, n = 0; R = H,R1 = R2 = OMe, n = 1) (II, III, IV, V), devoid of 1 or 2 MeO groups in positions 6 and 7. C6H6 (80 ml.) contg. 6.2 g. .beta.-cyclohexa-1,4-dienylethylamine stirred with cooling and dropwise addn. of freshly distd. 3,4-(MeO)2C6H3CH2COCl in 100 ml. C6H6 in the presence of 200 ml. 5% NaHCO3 and the amide kept in soln. by addn. of EtOAc, the mixt. stirred 2 hrs. at room temp. and the supernatant layer evapd. yielded 13.8 g. N-(3,4-dimethoxyphenylacetyl)-.beta.-cyclohexa-1,4-dienylethylamine (VI),

m. 111-12.degree. (C6H6C6H14). VI (2.0 g.) in 30 ml. C6H6 refluxed gently 30 min. with 2 ml. POCl3 and the solvent evapd. in vacuo, the residue taken up in dil. HCl and the soln. basified, the product (1.8 g.) refluxed 3 hrs. (N atm.) in 30 ml. xylene with 0.4 g. 30% Pd-C, the filtered soln. evapd. and the residue distd. in vacuo gave 1.65 g. viscous 1-(3,4-dimethoxybenzyl)-3,4-dihydroisoquinoline, b0.08 194-7.degree., .lambda. 271, 312, 323 m.mu. (log .epsilon. 3.81, 3.31, 3.33, alc.) [picrate m. 154-5.degree. (alc.)], also obtained by refluxing 6.0 g. N-(3,4-dimethoxyphenylacetyl)-.beta.-phenylethylamine 6.5 hrs. with 200 ml. xylene and 30 g. P2O5 and ***purifying*** the product by filtration through Al2O3. The base (2.0 g.) in 20 ml. Et cinnamate heated (N atm.) 2.5 hrs. over 0.2 g. 30% Pd-C and the cooled mixt. filtered, the filtrate and C6H6 washings shaken with 10% HCl and the ***acid*** soln. basified, the sirupy base (1.73 g.) ***chromatographed*** over Al2O3 in C6H6 and the product (1.52 g.) crystd. from C6H14 gave II, m. 71-2.degree., .lambda. 274, 311, 323 m.mu. (log .epsilon. 3.76, 3.49, 3.54, alc.); picrate m. 164.degree.(alc.). MeCH:CHPh (30 g.) in 250 ml. Et2O and aq. NaNO2 (120 g.) stirred and cooled with dropwise addn. of 410 g. 20% H2SO4 and the stirring contg. 1 hr., the product washed with H2O, MeOH and Et2O and dried yielded 26.3 g. corresponding pseudonitrosite (VII), m. 116-18.degree. (decompn.). VII (15 g.) added portionwise to 100 ml. 10% KOH in MeOH and the soln. ***neutralized*** with AcOH, the solvent evapd. in vacuo and the inorg. matter dissolved in H2O, the oily product taken up in C6H6 and the washed and dried soln. evapd. gave 12.5 g. PhCHMeCHMeNO2, b5 112-14.degree.. LiAlH4 (6 g.) in cold Et2O stirred with dropwise addn. of 13.8 g. nitro compd. in Et2O and dild. with cold H2O, the Et2O evapd. and the oily base taken up in HCl, shaken with C6H6 and basified with concd. NaOH, the C6H6 soln. dried and evapd. and the residue distd. (H atm.) in vacuo gave 8.8 g. PhCH(OMe)CHMeNH2, b6 93-5.degree.; HCl salt m. 186-8.degree. (alc. Me2CO). The amine (6.6 g.) in 18.3 g. abs. alc. and 100 ml. liquid NH3 reduced by portionwise addn. of 2.8 g. Li with cooling in alc. and solid CO2, the mixt. stirred until the blue color disappeared and the base distd. in vacuo (H atm.) yielded 5.2 g. 3-(cyclohexa-1,4-dienyl)-2-aminopropane (VIII), b5 71-2.degree.. Condensation of VIII with 3,4-(CH2O2)C6H3CH2COCl formed N-(3,4-methylenedioxyphenylacetyl)-.beta.-cyclohexa-1,4-dienylisopropylamine, m. 108-9.degree. (C6H14-C6H6), cyclized and dehydrogenated to 1-(3,4-methylenedioxybenzyl)-3-methyl-3,4-dihydroisoquinoline, 276, 318, 326 m.mu. (log 3.80, 3.46, 3.44, alc.) [picrate m. 170-1.degree. (decompn.)], further dehydrogenated in boiling PhCH: CHCO2Et by Pd-C to colorless prisms of III, m. 87-8.degree. (C6H14), .lambda. 278, 317, 329 m.mu. (log .epsilon. 3.89, 3.54, 3.56, alc.); picrate m. 180.degree. (alc. AcOH). Similarly condensation of VIII with 3,4-(CH2O2)C6H3COCl gave N-(3,4-methylenedioxybenzoyl)-.beta.-cyclohexa-1,4-dienylisopropylamine, m. 83-4.degree. (C6H14), cyclized and dehydrogenated to 1-(3,4-methylenedioxyphenyl)-3-methyl-3,4-dihydroisoquinoline, .lambda. 259 293 m.mu. (log .epsilon. 3.95, 3.83, alc.); picrate, m. 175-6.degree. (decompn.). Further dehydrogenation as for III yielded 72.5% IV, m. 74-5.degree. (C6H14), .lambda. 285, 333 m.mu. (log .epsilon. 3.96, 3.87, alc.); picrate, m. 184.degree. (alc.). Redn. of 4-MeOC6H4CH2CH2NH2 according to Birch (C.A. 52, 18525b) and distn. (H atm.) gave colorless .beta.-(4-methoxycyclohexa-1,4-dienyl)ethylamine, b1.0 78-8.5.degree., .lambda. 277 m.mu. (log .epsilon. 1.72), treated with 3,4-(MeO)2C6H3CH2COCl to yield 90.2% N-(3,4-dimethoxyphenylacetyl)-.beta.-cyclohexa-1,4-dienylethylamine (IX), m. 91-3.degree. (C6H6-C6H14). IX (2 g.) in 50 ml. C6H6 and 2 ml. POCl3 refluxed 10-15 min. on a steam bath and the cooled mixt. dild. with petr. ether, the base extd. with C6H6 and

shaken vigorously with 100 ml. 10% NaOH, the C6H6 layer dried over K2CO3 and the solvent evapd. (N atm.) in vacuo, the brown sirup refluxed 4 hrs. (N atm.) in abs. xylene over 0.5 g. 30% Pd-C and the filtered soln. evapd. in vacuo, the residue taken up in 10% HCl and extd. with C6H6, basified with NaOH soln. and the washed and dried ext. evapd. in vacuo, the residue filtered in C6H6-C6H14 through Al2O3 and the filtrate evapd. gave 0.21 g. 1-(3,4-dimethoxybenzyl)-7-methoxy-3,4-dihydroisoquinoline (X), .lambda. 277, 310, 321 m.mu. (log .epsilon. 3.83, 3.37, 3.89, alc.); picrate m. 159-61.degree. (decompn.) (Me2CO). Dehydrogenation of X yielded 60.4% V, m. 85-6.degree. (C6H14), .lambda. 277, 313, 323 m.mu. (log .epsilon. 3.85, 3.61, 3.63, alc.); picrate m. 171.degree. (alc. AcOH). The reddish oil, obtained by cyclizing IX with POCl3 acidified with 10% HCl and washed with C6H6, the ***acid*** soln. warmed several min. with C6H6 on a steam bath and the cooled mixt. basified with aq. Na2CO3, the washed and dried C6H6 layer concd. and the residue filtered through Al2O3, the filtrate evapd. and the base crystd. (C6H14-Me2CO) yielded 39.8% 1-(3,4-dimethoxybenzyl)-7-oxo-3,4,4a,5,6,7-hexahydroisoquinoline (XI), m. 176-8.degree., .nu. 1668 cm.-1 (Nujol); 2,4-dinitrophenylhydrazone sulfate m. 212-14.degree. (decompn.) (alc.). XI (0.6 g.)in 4 ml. CH(OMe)3 cooled and satd. with HCl, the mixt. refluxed 2.5 hrs. and excess CH(OMe)3 distd., the residue kneaded with 2 g. K2CO3 and covered with Et2O, cooled and treated with 20 ml. 5% K2CO3, the aq. layer extd. with Et2O and the product filtered in C6H6-C6H14 through Al2O3 gave 0.32 g. 1-(3,4-dimethoxybenzyl)-7,7-dimethoxy-3,4,-4a,5,6,7-hexahydroisoquinoline (XII); MeI salt m. 198-201.degree. (decompn.) (alc.). XII (0.25 g.) in a small amt. of C6H6 mixed with a few drops of (tert-BuO)3Al in C6H6 and the solvent evapd., the residue heated (N atm.) 2 hrs. at 200-20.degree. and extd. with C6H6, taken up in C6H14 and filtered through Al2O3, the filtrate evapd. and the oily product (0.11 g.) dehydrogenated in boiling PhCH:CHCO2Et over Pd-C gave 0.05 g. V, m. 85-6.degree..

L10 ANSWER 7 OF 13 CAPLUS COPYRIGHT 2001 ACS
AN 1958:98073 CAPLUS
DN 52:98073
OREF 52:17301g-i,17302a-i,17303a-i,17304a-i,17305a-g
TI Constitution of yohimbine and related alkaloids. X. Synthesis of 12H-indolo[2,3-a]pyridocolinium salts, including flavocoryline and flavopereirine
AU Prasad, K. B.; Swan, G. A.
CS Univ. Durham, Newcastle-upon-Tyne, UK
SO J. Chem. Soc. (1958) 2024-38
DT Journal
LA Unavailable
CC 10H (Organic Chemistry: Alkaloids)
GI For diagram(s), see printed CA Issue.
AB cf. C.A. 50, 13918g. In a new synthetic route to rings A, B, C and D of the yohimbine skeleton with or without ring E some 12H-indolo[2,3-a]pyridocolines salts (I) of indolo[2,3-a]pyridocolines (II) were synthesized, as well as a homolog (III) of alstyrine. Et2O (50 ml.) contg. 2.5 g. 2-NCC5H4N added in 10 min. with stirring at 0.degree. to EtO(CH2)3MgBr (1.2 g. Mg, 8 g. EtO(CH2)3Br, 30 ml. Et2O) and the mixt. refluxed 3 hrs., cooled to 0.degree., and stirred with gradual addn. of 20 ml. H2O and 70 ml. 5N H2SO4, the Et2O layer extd. twice with 70 ml. 2N H2SO4, the ***acid*** exts. heated 20 min. on a steam bath, the cooled soln. basified with satd. aq. K2CO3 and extd. with CHCl3, the ext. dried (K2CO3) and distd. (method A) gave 3.2 g. liquid imine (IV), 2-EtO(CH2)3C(:NH)C5H4N, b0.6 90-8.degree., b11 145.degree., .nu. 3376,

1681 cm.-1, also obtained (2.25 g.) by decompg. the Grignard complex with 30 ml. 1:1 concd. HCl-H2O and omitting the subsequent heating (method B). BuLi in Et2O (8 ml.) (1 ml. equiv. to 1.44 ml. N HCl) stirred at -50.degree. (N atm.) with addn. of 2 g. 2-BrC5H4N in Et2O and after stirring 15 min. treated with 2 g. EtO(CH2)3CN in Et2O, the mixt. kept 15 min. at -50.degree. and warmed gradually to room temp., stirred 1 hr. and dild. with 15 ml. H2O and 8 ml. 2N H2SO4, the Et2O layer worked up as above and the product (0.75 g.) distd. gave IV, b. 150.degree.. The samples of IV treated with warm alc. 2,4-(O2N)2C6H3NHNH2 contg. a few drops of HBr gave the HBr salt, m. 197.degree., converted by shaking with CHCl3 and dil. aq. Na2CO3 and evapg. the dried (Na2SO4) CHCl3 layer to 2-.gamma.-ethoxybutyrylpyridine 2,4-dinitrophenylhydrazone, m. 137.degree. (C6H6-petr. ether). IV (3 g.) refluxed 15 hrs. with 18 ml. AcOH and 9 ml. 47.5% HBr in a stream of N and the mixt. evapd. at 100.degree./14 mm., the residue taken up in a small vol. of MeOH and dild. with Me2CO gave 2.75 g. 1,2,3,4-tetrahydro-1-oxopyridocolinium bromide (V), m. 205.degree. (decompn.); picrate, m. 147-8.degree. (alc.); 2,4-dinitrophenylhydrazone, m. 192.degree. (decompn.) (alc.), 249-50.degree. (decompn.) (AcOH), giving with dil. NaOH a deep blue-violet color, sol. in CHCl3. V (1.5 g.), 0.9 g. PhNHNH2.HCl, and 3 g. cryst. NaOAc in sep. solns. in a min. of H2O heated together 3 hrs. on a steam bath and the cooled soln. filtered, the solid (2.1 g.) washed with H2O and crystd. (EtOH-Et2O) gave the bromide phenylhydrazone (Va), C15H16BrN3.0.5 H2O, m. 271.degree. (decompn.); IV phenylhydrazone picrate, C21H13N6O7, m. 225.degree. (decompn.) (HCONMe2-EtOH). Va (1.5 g.) in 45 ml. abs. alc. at 0.degree. satd. with dry HCl and kept 1 hr. at room temp., the mixt. refluxed 5 hrs. and kept overnight at 0.degree., filtered and the product washed with ice-cold alc. gave 1.2 g. 6,7-dihydro deriv. of I (VI, R = H, X = Cl) (VII), m. 340.degree. (decompn.) (MeOH-EtOH), .lambda.max. 2170, 2520, 31.40. 3850 A. (log .epsilon. 4.35, 3.93, 4.15, and 4.16), .lambda.min. 2390, 2745, 3410 A. (log .epsilon. 3.83, 3.42, 3.89) in alc. HCl; .lambda.max. 2230, 2645, 3630, 4200 A. (log .epsilon. 4.37, 4.40, 4.09, 4.19), .lambda.min. 2490, 2940, 3780 A (log .epsilon. 3.87, 3.55, 4.06) in 0.015N alc. KOH; picrate, m. 249.degree. (decompn.) (HCONMe2-MeOH); nitrate, m. 259.degree. (decompn.) (alc.). A Fischer indole reaction with the use of polyphosphoric ***acid*** according to Sugasawa, et al. (C.A. 51, 3593d), converted 2-MeC(:NNHPh)C5H4N into 2,2'-pyridylindole (VIII), heated 20 hrs. at 100.degree. with excess MeI and the mixt. dild. with Et2O to give VIII MeI salt, m. 238.degree. (MeOH). VII (80.6 mg.) in 10 ml. AcOH hydrogenated 4 hrs. at 18.degree./760 mm. with freshly reduced PtO2 and the warm filtered soln. evapd. at 100.degree./14 mm. gave the HCl salt, m. 302.degree. (decompn.) (alc.), basified in H2O with NaOH to give 1,2,3,4,6,7,12,12b-octahydro-12H-indolo[2,3-a]pyridocoline (IX), m. 150.degree. (ligroine) (cf. C.A. 46, 9569e). The ultraviolet absorption spectra in ***acid*** and alk. solns. were measured and corresponded with a change in structure. For comparison the spectra of VIII and 2,4'-pyridylindole and their respective MeI salts were shown. It was shown that the change in structure of VII in alk. soln. depended on the H atom attached to the indole-N atom. V (0.25 g.) treated with 0.17 g. PhNMeNH2 in the presence of 1.5 ml. N HCl and 0.75 g. NaOAc as above and the product ***isolated*** by addn. of satd. aq. KI gave 0.37 g. 1,2,3,4-tetrahydro-1-oxopyridocolinium 1-methyl-1-phenylhydrazone iodide, C16H18IN3, m. 203.degree. (alc.), subjected to a Fischer indole reaction and the soln. concd. to one third vol., kept at 0.degree. and the filtered soln. evapd. at 100.degree./14 mm., the residue taken up in H2O, the filtered soln. treated with satd. aq. KI, the ppt. washed with H2O and recrystd. (MeOH) to give VI (R = Me, X = I) (X), m. 295.degree.

(decompn.), .lambda.max. 2120, 2510, 3150, 3780 and .lambda.min. 2400, 2760, 3370 A. (log .epsilon. 2.60, 4.07, 4.10, 4.21, and 3.99, 3.38, 3.95, in ***acid***); .lambda.max. 2530, 3150, 3770 and .lambda.min. 2400, 2750, 3380 A. (log .epsilon. 4.06, 4.09, 4.19 and 3.97, 3.34, 3.92, in alkali), also obtained by treating aq. VII with 40% NaOH and filtering, washing the ppt. with cold H2O, and drying 2 days in vacuo, keeping the residue overnight with excess MeI, refluxing the mixt. 1 hr., evapg, and recrystg. (MeOH) the residue twice. The spectrum of X was almost identical with that of VII in ***acid*** soln. and did not change on addn. of alkali. Attempts to dehydrogenate VII by heating with acidic Pd-C according to Schwyzer (C.A. 47, 4347g) and by refluxing with chloranil in BuOH or shaking with O in AcOH in the presence of prereduced PtO2 were unsuccessful. IX (50 mg.) and 100 mg. acidic Pd-C heated to 260.degree. in 20 min. with evolution of H between 200 and 260.degree., the cooled mixt. extd. with MeOH, the ext. evapd., and the residue taken up in warm dil. HCl, the soln. basified with aq. NH4OH and extd. with Et2O, the dried ext. (K2CO3) evapd., and the oily residue recrystd. (C6H6-ligroine) (C) gave 20 mg. 1-butyl-.beta.-carboline, C15H16N2, m. 166.degree., .lambda.max. 2550, 2900, 3340, 3500, and .lambda.min. 2680, 3000, 3450 A (log .epsilon. 4.61, 4.24, 3.73, 3.75 and 3.73, 3.10, 3.68, in alc.), showing a blue-violet fluorescence in very dil. ***acid*** solns. (cf. Spenser, C.A. 51, 2785e). VII was successfully dehydrogenated by use of high-potential quinone according to Braude, et al. (C.A. 49, 13150c). VII (80 mg.) in 10 ml. alc. refluxed 15 hrs. with 0.4 g. tetrachloro-.omicron.-benzoquinone, the solvent evapd., and the residue crystd. (MeOH-Et2O) yielded 35 mg. I (R = H, X = Cl) (XI), C13H11ClN2.H2O, m. 295.degree. (decompn.), .lambda.max. 2440, 2940, 3450, 3880 and .lambda.min. 2680, 3050, 3770 A. (log .epsilon. 4.43, 4.12, 4.27, 4.10 and 3.96, 4.03, 4.05, in ***acid***); .lambda.max. 2270, 2410, 2890, 3200, 3490, 3700, 4490 and .lambda.min. 2370, 2620, 3100, 3280, 3600, 4180 A (log .epsilon. 4.42, 4.32, 4.43, 4.09, 4.26, 4.22, 3.63 and 4.30, 4.13, 4.02, 4.19, 3.57, in alkali); picrate, m. 252-3.degree. (decompn.) (HCONMe2-EtOH). The corresponding iodide prepd. as above for X and recrystd. (MeOH) 4 times gave I (R = H, X = I) (XII), m. 360.degree. (decompn.), .lambda.max. 2240, 2480, 2930, 3360, 3990 and .lambda.min. 2450, 2830, 3050, 3760 A (log .epsilon. 4.52, 4.31, 4.08, 4.27, 4.07 and 4.30, 4.01, 3.98, 3.96, in neutral soln.); .lambda.max. 2250, 2530, 3300, 4000 and .lambda.min. 2460, 2830, 3780 (log .epsilon. 4.51, 4.33, 4.27, 4.08 and 4.30, 4.05, 4.00, in alkali). The absorption spectra of XI in neutral and ***acid*** soln. corresponded to structures I and II, resp., and resembled very closely those of sempervirine under similar conditions. XI and VII showed a striking difference in dil. soln. under ultraviolet irradiation, the former and its homologs appearing brilliantly blue and the latter greenish-yellow. The slow disappearance of the 2390 A band on storage was considered to indicate the slow formation of a pseudo-base in alk. soln. II (R = R' = Et) (XIII) was synthesized by the above route from 2,4,5-NC(Et)2C5H2N (XIV). XIV [3 g., prepd. by improved modifications of the procedure of Lee and Swan (C.A. 50, 13918g)] treated with EtO(CH2)3MgBr (1.5 g. Mg and 10 g. EtO(CH2)2Br in 40 ml. Et2O) gave 2.8 g. imine, C15H24N2O, b0.2 132-40.degree., .nu. 3354 cm.-1; 2-.gamma.-ethoxybutyryl-4,5-diethylpyridine 2,4-dinitrophenylhydrazone hydrobromide, C21H27N5O5.HBr, m. 202.degree. (decompn.), ***neutralized*** to the corresponding base, C21H27N5O5, m. 109-10.degree. (C6H6-ligroine). The imine (1 g.) refluxed 21 hrs. with AcOH-HBr and the amorphous product taken up in a min. of H2O, basified with Na2CO3, and extd. with CHCl3, the dried (Na2SO4) ext. evapd., and the oil (0.8 g.) converted into 0.5 g. 7,8-diethyl-1,2,3,4-tetrahydro-1-

phenylhydrazonopyridocolinium bromide, m. 255.degree. (Et2O-EtOH), transformed (55 mg.) by the Fischer indole reaction to 35 mg. 2,3-diethyl-6,7-dihydro-12H-indolo[2,3-a]pyridocolinium chloride (XIVa), C19H21ClN2.1.5H2O, m. 273.degree. (decompn.) (alc.), .lambda.max. 2220, 3120, 3880 and .lambda.min. 2760, 3390 A (log .epsilon. 4.41, 4.19, 4.20 and 3.51, 3.94, in ***acid*** ; .lambda.max. 2300, 2630, 3610, 4110 and .lambda.min. 2520, 2920, 3740 A (log .epsilon. 4.44, 4.01, 4.13, 4.23 and 3.95, 3.50, 4.12, in alkali); picrate, m. 253.degree. (EtOH-Me2CO); nitrate, m. 262-3.degree. (EtOH). XIVa dehydrogenated with tetrachloro-.omicron.-benzoquinone gave 2,3-diethyl-12H-indolo[2,3-a]pyridocolinium chloride, C19H19ClN2.1.5 H2O, m. 258.degree. (decompn.) (EtOH-Et2O), .lambda.max. 2380, 2910, 3460, 3850 and .lambda.min. 2750, 3050, 3740 A (log .epsilon. 4.52, 4.15, 4.30, 4.24 and 4.04, 4.05, 4.16, in ***acid***); .lambda.max. 2310, 2410, 2880, 3180, 3640, 4400 and .lambda.min. 2370, 2650, 3090, 3260, 4190 A (log .epsilon. 4.43, 4.42, 4.44, 4.07, 4.31, 3.74 and 4.41, 4.14, 4.03, 4.05, 3.72, in alkali). Basification of the chloride in H2O and ***chromatography*** of the product in CHCl3 over Al2O3 gave XIII, C19H18N2.1.5 H2O, m. 150-1.degree. (MeOH); perchlorate, m. 301.degree. (decompn.), identical with flavocoryline perchlorate (cf. Goutarel, et al., C.A. 49, 10953i). II (R = iso-PrO, R' = Et) (XV) was also synthesized from 2,5,4-NC(Et)(iso-PrO)C5H2N (XVI). MeMgI (4.1 g. Mg, 24.3 g. MeI, and 125 ml. Et2O) treated dropwise with stirring in 10 min. with 10.8 g. 5,2,4-EtMe(AcO)C5H2N in 100 ml. Et2O at room temp. and the mixt. refluxed 3 hrs. with stirring, cooled in ice and decompd. with 210 ml. said NH4Cl soln. and 35 ml. concd. HCl, basified with 10% aq. NaOH and extd. with CHCl3, the dried (Na2SO4) ext. evapd. and the tertiary alc. (11.8 g.) refluxed 6 hrs. with 4.5 g. red P in 86 ml. 47.5% HI, the mixt. dild. with H2O and the filtered soln. basified with 20% aq. NaOH, extd. with CHCl3, and the dried (Na2SO4) ext. evapd. gave 9.2 g. XVI, b20 105-6.degree.; picrate, m. 179-80.degree. (alc.). XVI (10.5 g.) condensed with BzH by refluxing 96 hrs. in the procedure according to L. and S. (loc. cit.) yielded 10.5 g. 5,4,2-Et(iso-Pr)(PhCH:CH)C6H2N (XVII), b. 184-94.degree.; picrate, m. 235-6.degree. (decompn.) (alc.-HCONMe2). XVII (10.5 g.) oxidized and the BzOH removed, the soln. evapd. at 100.degree./14 mm. and the residue taken up in abs. alc., the filtered soln. evapd. and the residue in 150 ml. alc. satd. with dry HCl at 0.degree., the mixt. kept overnight at room temp. and refluxed 4 hr., the soln. evapd. at 100.degree./14 mm. and the cooled residue taken up in H2O, the soln. basified with satd. aq. Na2CO3 and extd. with CHCl3 gave 5.2 g. 5,4,2-Et(iso-PrO)C5H2NCO2Et (XVIII), b0.5 125-9.degree.; picrate, m. 111.degree. (alc.). XVIII (0.45 g.) refluxed 5 hrs. in 10 ml. alc. with 2.5 ml. 40% aq. KOH and the soln. evapd., washed with Et2O, adjusted to pH 4 with dil. HCl, extd. 30 hrs. with Et2O, and the ext. evapd. gave 0.23 g. 5,4,2-Et(iso-PrO)C5H2NCO2H, m. 147.degree. (MeOH-Et2O), unchanged by sublimation at 60-80.degree./0.01 mm., .lambda.max. 2670, 2340 and .lambda.min. 2525 A (log .epsilon. 3.64, 3.78 and 3.48). The ***acid*** heated with Cu powder and the dillate treated with picric ***acid*** gave 3,4-Et (iso-PrO)C5H3N.C6H3N3O7, m. 136-7.degree. (alc.) (cf. Karrer and Mainoni, C.A. 48, 2720i). XVIII (4.9 g.) shaken 72 hrs. with 49 ml. aq. NH4OH (d. 0.88) and the product (3.8 g.) sublimed at 60-80.degree./0.01 mm. gave 5,4,2-Et(iso-PrO)C5H2NCONH2, m. 164-5.degree., dehydrated in 3.5 hrs. to 2.75 g. 5,4,2-Et(iso-PrO)C5H2NCN (XVIIIa), b0.2 113-17.degree., converted by treatment with EtO(CH2)3MgBr to 5,4,2-Et(iso-PrO)C5H2NCO(CH2)3OEt (XIX), C16H25NO2, b2.0 165.degree.; 2,4-dinitrophenylhydrazone, m. 94.degree. (ligroine). XIX (1.15 g.) treated as above with HBr and the soln. evapd. gave 0.34 g. 2-.gamma.-bromobutyryl-5-ethyl-4-isopropylpyridine hydrobromide, m.

150-1.degree. (MeOH-Me2CO), which taken up in H2O the soln. basified with Na2CO3, extd. with Et2O, and the dried (K2CO3) ext. evapd. gave 7-ethyl-1,2,3,4-tetrahydro-1-phenylhydrazono-8-isopropylpyridocolinium bromide (XX), C20H26BrN3.0.5 H2O, m. 256-7.degree. (alc.-Et2O), also produced by evapg. the above MeOH-Me2CO mother-liquor and treating the residue with PhNHNH2. XX submitted to the Fischer indole reaction gave the 3,2-Et(iso-PrO) deriv. of VI (R = H, X = Cl) (XXI), C20H23ClN2. 0.5 H2O, m. 260.degree. (decompn.) (alc.-Et2O), .lambda.max. 2220, 3140, 3880 and .lambda.min. 2750, 3410 A (log .epsilon. 4.44, 4.25, 4.22 and 3.58, 3.97, in ***acid***); .lambda.max. 2310, 2660, 3600, 4110 and .lambda.min. 2520, 2910, 3770 A (log .epsilon. 4.45, 4.04, 4.16, 4.23 and 3.95, 3.41, 4.13, in alkali). Dehydrogenation of XXI with tetrachloro-.omicron.-benzoquinone yielded the corresponding 3,2-Et(iso-PrO) deriv. of I (R = H, X = Cl) (XXII), C20H21ClN2.H2O, m. 270.degree. (decompn.) (alc.-Et2O), .lambda.max. 2400, 2920, 3460, 3860 and .lambda.min. 2760, 3050, 3750 A (log .epsilon. 4.55, 4.15, 4.29, 4.25 and 3.99, 4.02, 4.16, in ***acid***); .lambda.max. 2310, 2890, 3180, 3610, 4420 and .lambda.min. 2620, 3090, 3280, 4180 A (log .epsilon. 4.43, 4.07, 4.30, 3.71 and 4.12, 4.01, 4.03, 3.67, in alkali). XXII in H2O basified yielded XV, C20H21ClN2.H2O, m. 117-19.degree. (alc.). XXI (0.2 g.) and 0.35 g. tetrachloro-.omicron.-benzoquinone heated 8 hrs. on a steam bath in 2.5 ml. AcOH, the cooled mixt. dild. with Et2O, filtered, the Et2O-washed residue taken up in CHCl3 and aq. NaOH, the dried (K2CO3) CHCl3 layer evapd., the residue taken up in alc. contg. HCl, the mixt. dild. with Et2O and filtered, the solid taken up in H2O, the soln. treated with NH4OH, the ppt. ***chromatographed*** in CHCl3 over Al2O3, and the product recrystd. from MeOH gave XV, m. 204, recrystd. (MeOH) to a product of apparently the same compn., m. 149.degree. (for comparison of XV with flavocorynanthryrine, cf. Schwyzer, loc. cit.). The alkaloid flavopereirine, assigned the structure II (R = H, R' = Et) (XXIIa) by Bejar, et al. (C.A. 51, 14768c), was synthesized from 2,5-NCEtC5H3N (XXIII). XXIII (1.77 g.) treated with EtO(CH2)3MgBr gave 1.77 g. 5,2-EtC5H3NCO(CH2)3OEt, b3 150-60.degree., converted (1.65 g.) with HBr and further treatment to 1.22 g. pyridocolinium bromide phenylhydrazone, m. 279.degree. (alc.-Et2O). The Fischer indole reaction transformed 0.5 g. hydrazone to 0.33 g. chloride (XXIV), converted to the 3-Et deriv, of VI (R = H, X = NO3), C17H17N3O3, m. 267.degree. (decompn.) (alc.), .lambda.max. 2130, 2520, 3160, 3950, and .lambda.min. 2430, 2750, 3450 A. (log .epsilon. 4.41, 3.95, 4.21, 4.16, and 3.88, 3.55, 3.92, in ***acid***), .lambda.max. 2220, 2670, 3600, 4230, and .lambda.min. 2490, 2950, 3830 A. (log .epsilon. 4.40, 4.01, 4.09, 4.21, and 3.83, 3.32, 4.05, in alkali). XXIV (0.13 g.) heated 9 hrs. on a steam bath with 0.23 g. tetrachloro-.omicron.-benzoquinone in 2 ml. AcOH and worked up as above, the dehydrogenated chloride tn up in MeOH, and treated with HClO4 gave 38 mg. authentic XXIIa perchlorate, C17H15ClN2O4.HClO4, m. 331.degree. (decompn.), .lambda.max. 2350, 2950, 3500, 3900, and .lambda.min. 2730, 3090, 3820 A. (log .epsilon. 4.52, 4.21, 4.32, 4.20, and 4.03, 4.07, 4.16, in ***acid***), .lambda.max. 2300, 2350, 2890, 3200, 3600, 4500, and .lambda.min. 2320, 2670, 3100, 3300, 4200 A. (log .epsilon. 4.46, 4.45, 4.49, 4.10, 4.33, 3.68, and 4.44, 4.14, 4.08, 4.05, 3.62, in alkali). The availability of XVIIIa provided an opportunity for the synthesis of III, 3-ethyl-2-(5-ethyl-4-isopropyl-2-pyridyl)indole. XVIIIa (0.81 g.) treated with PrMgBr gave 0.3 g. 5,4,2-Et(iso-PrO)C5H2NCOPr, b1.0 80-90.degree., converted by Fischer indole synthesis to material, b0.3 184-95.degree. triturated with ligroine and recrystd. (MeOH and petr. ether) to give III, C20H24N2, m. 103-4.degree.; HCl salt, m. 221-3.degree. (decompn.)

(MeOH-EtOAc), .lambda.max. 3260 A. (log .epsilon. 4.30), .lambda.min. 2730 A. (log .epsilon. 3.61) (alc.); picrate, m. 211-13.degree. (alc.-HCONMe2). Following the speculation of Boekelheide that highly potent calabash curares might contain a hexahydrobenzindolopyridocoline nucleus the synthesis of various related compds. was undertaken. Excess MeI and the appropriate base kept overnight in C6H6 and the ppt. crystd. (MeOH) gave 5,7,8,13,13b,14-hexahydrobenz[g]indolo[2,3-a]pyridocoline methiodide, C19H18N2.MeI, m. 279.degree. (decompn.), refluxed with excess AgCl in dil. MeOH and recrystd. (MeOH-Me2CO) to give the corresponding methochloride (XXV), orange-yellow with concd. HNO3, yellow in concd. H2SO4 changed to red with a drop of H2O and to intense blue-purple with K2Cr2O7; methopicrate, m. 199.degree. (MeOH). XXV had less than 10% activity of d-***tubocurarine*** . Attempts to synthesize 8,9-dihydro-14H-benz[h]-and 6,7-dihydro-12H-benz[f]indolo-[2,3-a]pyridocolinium chlorides from 1-cyanoisoquinoline (XXVI) and 2-cyanoquinoline (XXVII) by the general method failed since the phenylhydrazones of the bromides (XXVIII and XXIX) were recovered unchanged from an attempted Fischer indole reaction. XXVI (2.7 g.) treated with EtO(CH2)3MgBr gave 2.2 g. 1-(.gamma.-ethoxybutyryl)isoquinoline, b2 170-5.degree.; 2,4-dinitrophenylhydrazone, m. 163.degree. (alc.).

The ketone (1.09 g.) treated with HBr gave 0.8 g. XXVIII, 1,2,3,4-tetrahydro-1-oxobenzo[a]pyridocolinium bromide, C13H12BrNO, m. 223-4.degree. (alc.-Me2CO), reduced according to Clemmensen to a base, C13H17N; picrate, m. 184.degree. (decompn.). XXVIII (0.8 g.) treated with PhNHNH2 gave 0.7 g. phenylhydrazone bromide, m. 279.degree. (alc.-Et2O), converted to the corresponding chloride, C10H18ClN3.2H2O, m. 243-6.degree. (alc.-Et2O), .lambda.max. 2430, 2650, 4490, and .lambda.min. 2600, 3600 A. (log .epsilon. 4.65, 4.06, 4.41, and 4.04, 3.00, in ***acid***), .lambda.max. 2300, 2440, 3300, 5120, and .lambda.min. 2380, 3020, 3760 A. (log .epsilon. 4.38, 4.38, 3.78, 4.44, and 4.36, 3.60, 3.22, in alkali); phenylhydrazone nitrate, m. 237.degree. (alc.); phenylhydrazone picrate, m. 200.degree. (alc.-HCONMe2). XXVII [2.6 g. prepd. according to Henze (C.A. 31, 57999)] treated with EtO(CH2)3MgBr by methods A and B for IV gave, resp., 2.2 g. imine, b0.5 165.degree., .nu. 3343 cm.-1, and 2 g. 2-(.gamma.-ethoxybutyryl) quinoline, b2 190.degree.; 2,4-dinitrophenylhydrazone, m. 148.degree.. The imine or ketone (1.9 g.) refluxed 21 hrs. with AcOH-HBr yielded 1.6 g. XXIX, 1,2,3,4-tetrahydro-4-oxobenzo[c]pyridocolinium bromide, C13H12BrNO.3H2O, m. 116-18.degree. (MeOH-Me2CO); phenylhydrazone bromide, m. 251-2.degree. (alc.-Et2O); phenylhydrazone chloride, m. 257-8.degree. (alc.-Et2O), .lambda.max. 2280, 2680, 3270, 4570, and .lambda.min. 2500, 2900, 3670 A. (log .epsilon. 4.13, 3.96, 3.62, 4.35, and 3.86, 3.43, 3.24, in ***acid***), .lambda.max. 2290, 4890, and .lambda.min. 3390 A. (log .epsilon. 4.14, 4.27 and 2.97, in alkali); phenylhydrazone nitrate, m. 257-8.degree. (alc.); phenylhydrazone picrate, m. 245.degree. (decompn.) (alc.-Me2CO).

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TI Muscarine. V. Indirect proof of the constitution of muscarine by synthetic investigations
AU Eugster, C. H.; Waser, P. G.
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SO Helv. Chim. Acta (1957), 40, 888-906
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LA Unavailable
CC 10 (Organic Chemistry)
AB Synthetic investigations into the structure of muscarine, previous to and in support of the formula proposed by Kogl, et al. (C.A. 51, 12058e), are reported, and the syntheses of substituted .beta.-aminotetrahydrofurans and their quaternary salts from .gamma.-lactones, .alpha.-acetylenic ketones, and 3-furancarboxylic acids are described. Me 4,5-dihydro-3-furancarboxylate (28.63 g.) hydrogenated with 1.5 g. 5% Pd-BaSO4 in MeOH at room temp. and pressure, the mixt. filtered, the filtrate evapd. carefully, and the residue distd. yielded 83% Me tetrahydro-3-furancarboxylate (I), b12 61-5.degree.. I (18.5 g.) in 30 cc. abs. EtOH treated with 7.1 g. N2H4.H2O, the warm soln. refluxed 1 hr., the solvent evapd., and the residue distd. at 100-10.degree./0.01 mm. gave the hydrazide, m. 85.5-7.0.degree.. The hydrazide in 80 cc. 2N HCl layered with Et2O, the cooled mixt. stirred with dropwise addn. of 12.1 g. KNO2 in a small amt. of H2O, the aq. layer extd. 5 times with Et2O, the combined exts. and the Et2O layer cooled by addn. of solid CO2, the ext. washed with aq. NaCl, dried over MgSO4, filtered, the filtrate concd. to 1/4 vol., dild. with 50 cc. C6H6, evapd. to 1/3 vol., the azide soln. treated with 20 cc. abs. PhCH2OH, warmed to 40-50.degree. with addn. of Pt tetrahedra, the temp. raised carefully to complete the evolution of N, the mixt. refluxed 3 hrs., the solvent evapd. in vacuo, the residue crystd. from Et2O, filtered, the mother liquor evapd., and the residue distd. at 120-35.degree./0.02 mm. gave 21.14 g. benzylurethan, m. 60-1.degree. (from petr. ether). The benzylurethan (20.92 g.) hydrogenated with 0.5 g. 5% Pd-BaSO4 and further addn. of 2 portions of 0.2 g. Pd-C, filtered, the filtrate ***neutralized*** with N HCl, the solvent evapd. in vacuo, the residue taken up in a small amt. of H2O, the soln. layered with much Et2O, the H2O taken up by addn. of sufficient powd. KOH, the Et2O decanted, the residue extd. several times with boiling Et2O, the combined exts. dried over KOH, evapd., and the residue distd. gave 6.31 g. .beta.-aminotetrahydrofuran (II), b59 73.degree., readily sol. in H2O to a strongly alk. soln. reducing AuCl3 in 0.1N HCl, Fehling soln., and ammoniacal AgNO3 on warming, and giving a white ppt. with Nessler reagent. II (4.293 g.), 9.4 g. 35% HCHO, and 6.80 g. 99% HCO2H heated 10 hrs. at 100.degree., treated with 26 cc. 2N HCl, the soln. evapd. in vacuo, and the residue sublimed at 110-20.degree./0.01 mm. gave 6.212 g. HCl salt, m. 140.degree. (from MeOH-Me2CO), converted as above to N,N-dimethyltetrahydro-3-furylamine, b80 77-8.degree.; MeI salt, m. 226.0-6.5.degree. (from EtOH-Et2O); Me Cl salt (IIa), m. 298-9.degree. (decompn.); MeAuCl4 salt, m. 228-9.degree. (decompn.). HCO2Et (85 g.) and 123 g. .gamma.-caprolactone in Et2O were condensed in the presence of 25 g. Na powder according to Korte and Machleidt (C.A. 50, 16760b), and the crude product was rearranged with MeOH-HCl to an isomeric mixt. of 3-carbomethoxy-5-ethyl-2-methoxytetrahydrofurans, b12-13 95-101.degree., cleaved by treatment with 20 drops of concd. H2SO4 to 73.07 g. 4-carbomethoxy-2-ethyldihydrofuran, b12-13 89-92.degree., .lambda. 254 m.mu. (.vepsiln. 10,000 in EtOH). The ester (71.4 g.) hydrogenated with 5 g. 5% Pd-BaSO4 in 200 cc. MeOH at room temp. and pressure, the mixt. filtered through Norit-Celite, evapd., the residue reduced in AcOH with 1 g. PtO2, filtered, and the AcOH carefully evapd. over a glass-ring ***column*** gave 56.3 g. 4-carbomethoxy-2-ethyltetrahydrofuran (III), b13 87-8.degree.. III (52 g.) and 16.5 g. N2H4.H2O in 80 cc. alc. refluxed 1 hr., treated with 2.0 g. N2H4.H2O, refluxed 1 hr., the solvent evapd. in vacuo, and the product distd. in a high vacuum gave the hydrazide, C7H14N2O2, b0.02 120-30.degree., m. 60.degree. (from CHCl3-Et2O and sublimation). The crude hydrazide in 165 cc. 2N HCl was stirred at

0.degree. with 22.7 g. NaNO2 in 50 cc. H2O and the mixt. worked up as above. The azide carefully heated with 35.5 PhCH2OH in 50 cc. C6H6 to 45.degree. in 30 min., the temp. raised and, after cessation of N evolution, the mixt. refluxed 2.5 hrs., the solvent evapd., and the residue distd. gave 38 g. benzylurethan, b0.1-0.05 130-40.degree., m. 49.5-50.5.degree. (from Et2O at -80.degree.), reduced by 2 g. Pd-BaSO4 in MeOH at room temp. and pressure, with addn. of 400 mg. Pd-C at the end of the reduction. The filtered reduction mixt. dild. with 200 cc. N HCO2H, evapd. in vacuo, the thick sirup heated 8 hrs. at 100.degree. with 59.3 g. 38% HCHO and 39.8 cc. 98% HCO2H, the cooled mixt. treated with 76 cc. 2N HCl, evapd. in vacuo, the residue taken up in a small amt. of H2O, extd. with Et2O, the aq. soln. made strongly alk. with 50% KOH, exhaustively extd. with CHCl3, the washed and dried ext. evapd., and the residue distd. through a 10-cm. Vigreux ***column*** gave 11.9 g. 4-amino-2-ethyltetrahydrofuran (IV), b12 62.5-3.0.degree., quaternized with MeI in Et2O to the MeI salt, m. 142-4.degree. (from iso-PrOH); MeCl salt (IVa), m. 151-2.degree. (from iso-PrOH-Et2O); MeAuCl4 salt, m. 116-18.degree. (from H2O). Pyranyl propargyl ether (81.5 g.) in 250 cc. dry Et2O treated dropwise with stirring and cooling (N atm.) in 2 hrs. with BuLi in Et2O (11.7 mg. Li/cc.), the yellow soln. stirred 2 hrs. at 0.degree., the cooling system removed, the stirring continued until room temp. was reached, the soln. transferred (N atm.) dropwise in 90 min. with stirring to 100 g. pure (EtCO)2O in 100 cc. dry Et2O at -80.degree., brought to room temp., kept overnight, externally cooled with ice, cautiously decompd. with H2O, the Et2O layer and Et2O washings of the aq. layer washed with H2O, NaHCO3, and NaCl soln., the dried ext. evapd., and the residue distd. gave 58.5 g. 2-hexyn-4-on-1-yl .alpha.-pyranyl ether, b0.04 64-6.degree., .lambda. 218 m.mu. (.epsilon. 7250, EtOH). The acetylene ketone (24.6 g.) in 100 cc. dry Et2O at -30.degree. treated dropwise with 10 cc. anhyd. NHMe2, the mixt. kept 14 hrs. at 0-10.degree., evapd., and a sample of the residual oil (29.2 g.) distd. gave 2-dimethylamino-2-hexen-4-on-1-yl .alpha.-pyranyl ether, b0.02 110.degree., .lambda.max. 322, .lambda.shoulder 226, .lambda.min. 255 m.mu. (log .epsilon. 4.36, 3.29, 2.58, EtOH). The crude ketone (29.2 g.) hydrogenated in AcOH with 1 g. PtO2, the mixt. filtered, the filtrate evapd., the oily residue taken up in H2O, extd. with Et2O, the aq. soln. adjusted to pH 12 with NaOH, exhaustively extd. with Et2O, the basic residue (14.5 g.) cyclized by heating 1 hr. at 100.degree. with 75 cc. H3PO4 (d. 1.7) and 230 cc. H2O, the cooled soln. steam-distd., the distillate ***neutralized*** with HCl, the soln. evapd. in vacuo, the residue taken up in a small amt. of H2O, the soln. adjusted to pH 14 with KOH, extd. with Et2O, the dried ext. evapd. and the residue distd., gave 6 g. oily IV. Similarly [MeCH(OMe)-CO]2O, b10 97-9.degree., .nu. 1757, 1835 cm.-1, was converted through the methoxylated acetylene ketone, C14H25O4, b0.05 100.degree., .lambda. 221 m.mu. (.epsilon. 5050, EtOH), to the amino ketone, C14H25NO4, b0.02 140-5.degree., .lambda. 322 m.mu. (.epsilon. 22750, EtOH), reduced with LiAlH4 to the unsatd. amino alc., C14H27NO4, b0.02 110-15.degree., .lambda. 234 m.mu. (log .epsilon. 3.58, EtOH), and further reduced with 5% Pd-BaSO4 in EtOH to the satd. amino alc., b0.04 80-100.degree.. The cyclization of this isomeric mixt. was unsatisfactory. 3-Furoic ***acid*** (75.5 g.) (prepd. by decarboxylation of furantetra-carboxylic ***acid*** according to Smith, et al., C.A. 46, 4338f) in 83 cc. abs. MeOH and 208 cc. (CH2Cl)2 boiled 15 hrs. with 1.97 cc. concd. H2SO4, treated with 20 cc. MeOH and 0.5 cc. concd. H2SO4, boiled 2 hrs., the cooled soln. dild. with the same vol. of Et2O, extd. with aq. NaHCO3, and the org. layer dried and carefully evapd. gave 68.13 g. Me 3-furoate, b42 78-80.degree.. The ester

(51.9 g.) and 45 cc. Ac2O at 50.degree. treated with 5.5 g. BF3-Et2O complex, the soln. heated in 5 min. to 95.degree., the heating stopped, the mixt. at 60.degree. cooled externally with ice, the cold mixt. decompd. with H2O and excess Et2O, the Et2O soln. washed with H2O and Na-HCO3, dried, evapd., and the residue distd. gave 31.27 g. Me 5-acetyl-3-furoate (V), b11 115-30.degree. (pure product, b11 128-9.degree.), m. 88.5-9.0.degree. (from Me2CO-petr. ether), .lambda. 263 m.mu. (.epsilon. 13,240, alc.); p-nitrophenylhydrazone, m. 238.5-9.5.degree.. Sublimed 3-furoic ***acid*** (36.81 g.) heated to 60.degree. in 40 cc. Ac2O, treated with 4 cc. BF3-Et2O, quickly heated to and maintained 15 min. at 125.degree., the cooled mixt. shaken with 20 cc. 2N AcOH, evapd. in vacuo, the residue taken up in H2O, treated with Norit, filtered hot, the filtrate dild. with an equal vol. of Me2CO, filtered through 120 g. Al2O3 (Woelm, ***acid***), the ***column*** washed with 1 l. 1:1 Me2CO-H2O, the combined eluates evapd. in vacuo, the mixt. sublimed at 0.02 mm., and the crude product crystd. from H2O gave 17.5 g. 5-acetyl-3-furoic ***acid*** (Va), m. 208.0-9.5.degree., .lambda.max. 205, 265, .lambda.min. 219 m.mu. (.epsilon. 13,600, 12,720, 2100, EtOH). Va (500 mg.) in 10 cc. ice-cold 2N NaOH treated dropwise with 850 cc. 0.1N KMNO4 until the violet color persisted 5 min., the soln. heated, filtered, the filtrate evapd. in vacuo, the residue taken up in a small amt. of H2O, the soln. extd. with Et2O, the aq. soln. acidified, extd. exhaustively with Et2O, the ext. evapd., the residue sublimed, the sublimate crystd. from H2O, and the cryst. product sublimed gave 20 mg. 2,4-furandicarboxylic ***acid*** , m. 268.degree., .lambda.max. 240, .lambda.min. 215 m.mu. (log .epsilon. 4.02, 3.67, H2O). V (31.19 g.) in 200 cc. 1:1 EtOH-EtOAc reduced with 5 g. 5% Pd-BaSO4, the mixt. filtered through a layer of Celite, the filtrate evapd. in vacuo, the residue in 150 cc. MeOH completely reduced in 2 hrs. with 3 g. prereduced PtO2 in 50 cc. AcOH, the mixt. filtered, the filtrate evapd. in vacuo, and the residue distd. gave 29.65 g. Me 5-(.alpha.-hydroxyethyl)tetrahydro-3-furancarboxylate (VI), b10 130-6.degree.. VI (27.5 g.) in 50 cc. abs. alc. treated with 8.00 g. N2H4.H2O, the mixt. refluxed 1 hr., evapd., the crude hydrazide taken up in 76 cc. 2.28N HCl, dild. with 50 cc. Et2O, the ice-cold mixt. stirred with dropwise addn. of concd. aq. NaNO2 (12.0 g.), adjusted to pH 1.0 with HCl, the Et2O layer cooled with solid CO2, the aq. layer extd. 7 times with 60 cc Et2O, the combined dry exts. evapd. to 1/4 vol., treated with 100 cc. C6H6, the mixt. evapd. to 1/3 vol., dild. with C6H6, reevapd., the clear yellow azide soln. slowly heated on a steam bath with 50 cc. freshly distd. PhCH2OH, finally refluxed 6 hrs., the solvent and PhCH2OH evapd. in vacuo, and the residue distd. gave 15-60 g. benzylurethan, b0.04 155-65.degree., which was hydrogenated with 2 g. 5% Pd-BaSO4 and 500 mg. Pd-C, the mixt. filtered, the filtrate evapd., the residue taken up with ice cooling in 11.1 g. 38% HCHO and 13.5 g. 98% HCO2H, the soln. refluxed 6 hrs., the cooled mixt. concd., the concentrate treated with excess 40% KOH, extd. with CHCl3, the dried ext. evapd., and the residue distd., giving 6.35 g. N,N-dimethyl-2-(.alpha.-hydroxyethyl)tetrahydro-4-furylamine (VII), b. 110-15.degree.; picrate, m. 109-13.degree. (from alc.). VII (2.50 g.) in 20 cc. Et2O treated with 2 cc. MeI, refluxed several hrs., and the oily product triturated with Me2CO gave the cryst. MeI salt, m. 137-47.degree., converted with AgCl into the hygroscopic chloride, which, dried in a high vacuum and crystd. from iso-PrOH-Me2CO, yielded an isomeric mixt. of VII MeCl salts, m. 149-51.degree.; the mixt. (3.847 g.) in a min. of solvent 16 (cf. C.A. 51, 355i) ***chromatographed*** on 1.47 kg. cellulose powder pre-washed with solvent 16, the ***column*** eluted wtih the same solvent to give 300 fractions of 1000 drops, fractions 122-37 and 157-270 combined,

evapd., the residue taken up in H2O, acidified with HCl, the ***acid*** solns. clarified with Norit, evapd., the residues taken up in abs. alc., filtered, the filtrates, evapd., and the residues crystd. from iso-PrOHMe2-CO gave isomer (VIIA.MeCl), m. 140-2.degree. (MeBPh4 salt, m. 214.5-16.5.degree.; MeAuCl4 salt, m. 114.5-15.0.degree.; reineckate, m. 145-6.degree.), and isomer (VIIB.MeCl), m. 175.5-6.0.degree. (Me-BPh4 salt, m. 196.0-6.5.degree.; MeAuCl4 salt, m. 151.0-2.5.degree.). Va (2.140 g.) heated 1.5 hrs. with 5 cc. pure SOCl2 at 110.degree., the excess SOCl2 evapd., and the residue distd. gave 950 mg. ***acid*** chloride, converted by treatment in 5 cc. Et2O at 0.degree. with 1.2 g. NaN3 in H2O to the cryst. azide, ***purified*** by taking up in CHCl3 or Me2CO, sepg. the H2O layer, filtering, and evapg. in vacuo. The pure cryst. azide treated with 5 cc. 98-9% HCO2H, carefully heated in the presence of Pt tetrahedra to 80-5.degree., maintained 1 hr., heated 10 min. to 100.degree., the soln. evapd. in vacuo, the residues taken up in hot H2O, decolorized with Norit, filtered hot, the cooled soln. filtered, and the almost colorless cryst. residue sublimed at 130-50.degree./0.04 mm. gave 292 mg. pure 5-acetyl-3-formamidofuran (VIII), m. 190-1.degree., .lambda.max. 229, 295, .lambda.min. 263 m.mu. (.epsilon. 14,900, 8160, 2730, alc.). VIII (20.2 mg.) hydrogenated 165 min. with 9.34 cc. H in 5.00 cc. MeOH in the presence of 20.3 mg. brown Pd oxyhydrate-BaSO4 (cf. Kuhn and Haas, C.A. 50, 3675d) and the product distd. gave 3-formamido-5-(.alpha.-hydroxyethyl)tetrahydrofuran (IX), b0.02 100-20.degree.. IX (150 mg.) in ice-cold tetrahydrofuran added dropwise to 210 mg. Li-AlH4 in 5 cc. Et2O, the mixt. refluxed, kept 14 hrs. at room temp., decompd. with H2O, filtered through Celite, the filtrate evapd., and the residue distd. gave 140 mg. 5-(.alpha.-hydroxyyethyl)-3-(methylamino)tetrahydrofuran (X), b0.08 90-100.degree., quaternized in alc. with 0.2 cc. MeI and 1.0 cc. N KOH by boiling 1 hr., acidifying with HCl, evapg. in vacuo, extg. the residue with alc., filtering, and evapg. to give 162 mg. mixt. of VIIA.- and VIIB.MeCl. VIIA.MeCl (42.8 mg.) in 5.00 cc. H2O oxidized 26 min. with 80 mg. PtO2, the mixt. filtered, the filtrate evapd., and the residue crystd. from iso-PrOH-Et2O gave trimethyl(2-acetyl-4-tetrahydrofuryl)ammonium chloride (XI), m. 186-9.degree., also obtained by oxidation of VIIB.MeCl, ***purified*** by recrystn. of the mixed XI from iso-PrOH-Et2O and drying at 100.degree./0.02 mm. to give XI, C9H18ClNO2.1/3H2o, m. 185.5-7.0.degree., .nu. 1709 cm.-1 (Nujol); MeAuCl4 salt, m. 119-20.degree. (from H2O), .nu. 1709 cm.-1 (Nujol). Pure muscarine chloride (XII) (19.3 mg.) (from I. patouillardi) in 5.00 cc. H2O oxidized 12 hrs. with 40 mg. prereduced PtO2, the mixt. filtered, and the filtrate boiled 1 hr. with 200 mg. Ag2O in the app. of Wiesenberger (C.A. 41, 3017d) gave a distillate ***neutralized*** by less than 0.2 cc. 0.05N HCl (methyl red). XII (19.6 mg.) similarly oxidized 14 hrs. with 100 mg. PtO2 in 0.1N AcOH, the mixt. filtered, the filtrate evapd. in vacuo, the residue taken up in ice-cold H2O, treated with excess HAuCl4, filtered, and the residue dried in a high vacuum gave oxomuscarine tetrachloroaurate, m. 89-93.degree., .nu. 1752 cm.-1 (Nujol). Oxomuscarine chloride (XIII), [.alpha.]D24 3.9.degree. (c 5.08, alc.), .lambda. 279 m.mu. (.epsilon. 139, H2O), .nu. 1754 cm.-1, Rf in solvents 14 and 16 similar to those of XII, giving a red color with Dragendorff reagent, reducing HAuCl4 in the presence of alkali and Fehling soln. on heating, and giving no reaction with triphenyltetrazolium chloride and Schiff reagent. XIII reduced with KBH4 in MeOH, decompd. with HCl, the mixt. evapd. in vacuo, and the residue extd. with alc. gave a product with Rf 0.24 in solvent 16 (XII, VIIA.MeCl, VIIB.MeCl showed Rf 0.25, 0.20, 0.16, resp.). trans-Trimethyl(2-hydroxycyclopentyl)ammonium chloride (790 mg.) [from the iodide with AgCl

(cf. Friess and Baldridge, C.A. 50, 16926h)] in 5.00 cc. H2O oxidized 14 hrs. with Pt from 1.00 g. PtO2, and the mixt. worked up gave the unstable quaternary oxo chloride, converted into the more stable tetrachloroaurate, m. 160-70.degree. (decompn. with cleavage of NMe3) (from alc.), .nu. 1751 cm.-1 (Nujol). The infrared spectrum of XIII indicated the presence of a 5-membered ring. The behavior of XIII in the presence of alkali showed that the NMe3 group is not in the .alpha.- or .beta.-position to the CO group and accordingly I has the structure proposed by Kogl, et al. (loc. cit.). The pharmacol. testing of IIa. IVa, VIIA.MeCl, and VIIB.MeCl on frog and cat prepns, showed nicotine- and ***curare*** - but less muscarinelike activity than that of I.

L10 ANSWER 9 OF 13 CAPLUS COPYRIGHT 2001 ACS
AN 1957:81536 CAPLUS
DN 51:81536
OREF 51:14759i,14760a-i,14761a-i,14762a-h
TI Constitution of athamantin and oroselol
AU Halpern, O.; Waser, P.; Schmid, H.
CS Univ. Zurich, Switz.
SO Helv. Chim. Acta (1957), 40, 758-78
DT Journal
LA Unavailable
CC 10 (Organic Chemistry)
GI For diagram(s), see printed CA Issue.
AB Exptl. proof was sought for the clarification of the doubtful structure of athamantin (I) (cf. Spath and S., C.A. 35, 47526). Dry I (300 mg.) in 10 ml. N NaOMe kept 22 hrs. at 4-10.degree., the yellow soln. satd. with CO2, the solid mixt. dild. with CO2-satd. H2O and satd. with CO2, the cloudy mixt. repeatedly ext. with Et2O-C5H12, the org. ext. washed with H2O, 2:1 satd. NaHCO3-Na2CO3, and aq. NaCl soln., the dried ext. evapd. and the cryst. residue (229.4 g.) ***chromatographed*** on a 20-fold amt. of neutral Al2O3 (dried at 110.degree. and treated with 5% H2O), eluted with 1:1 C6H6-C5H12, and the fraction recrystd. from C5H12-Et2O or C5H12-C6H6 gave 123 mg. compd. A (II), m. 104-5.degree., [.alpha.]D20 0.00 .+-. 0.02.degree. (c 1.2, MeOH), .lambda. (max.) 218, 249, 257, 285, 293 (shoulder), (min.) 234, 253, 269 m.mu. (log .epsilon. 4.52, 4.18, 4.22, 3.51, 3.46, 3.81, 4.13, 3.30, in 96% alc.), intense blue in Gibbs test, colorless soln. in dil. NaOH. Dry I (600 mg.) refluxed 3 hrs. in 15 ml. N NaOMe (dry atm.), the intense yellow soln. ***neutralized*** with excess AcOH at 0.degree. and evapd. in vacuo, the residue taken up in H2O, the soln. kept 30 min.-1 hr. and shaken out with Et2O, the Et2O ext. extd. 5 times with 3-ml. portions 1:1 satd. NaHCO3-Na2CO3 solns. and exhaustively with ice-cold 0.5% aq. KOH, the alk. exts. acidified to pH 5 [ext. P (III)], the Et2O ext. washed with aq. NaCl, the dried ext. evapd., and the cryst. residue (61.5 mg.) distd. at 150-60.degree./0.02 mm. and recrystd. from C5H12-Et2O and C5H2-C6H6 gave furocoumarin C (IV), m. 116-17.degree., .lambda. (max.) 215, 251, 301, (min.) 230, 272 m.mu. (log .epsilon. 4.22, 4.48, 4.06; 4.00, 3.64) [2,4-dinitrophenylhydrazine deriv. (IVa), m. 208-10.degree. (from EtOAc)], blue-green Gibbs test, oxidized with CrO3 to AcOH only (cf. C.A. 48, 10491g; 50, 4986b), pos. lactone ring test. III satd. with NaCl and extd. with Et2O, the ext. washed with NaHCO3 and NaCl solns., the dried ext. evapd., the cryst. residue (273 mg.) taken up in 3:1 C6H6-Et2O and filtered through 1 g. washed silica gel, and the evapd. eluate recrystd. from Et2O-petr. ether and C6H6-petr. ether gave 130 mg. 2-(1-methyl-1-methoxylethyl)-4-hydroxy-5-(2-carbomethoxyvinyl)benzofuran (V), m. 156-7.degree., .lambda. (max.) 224, 251, 296, 334, (min.) 230, 274, 328 (log .epsilon. 4.11, 4.49, 4.23, 3.90,

4.09, 3.95, 3.89), yellow soln. in 0.5% KOH, no FeCl3 reaction, blue-green Gibbs reaction, giving only AcOH on CrO3 microoxidation. I (800 mg.) boiled 3 hrs. with 20 ml. N NaOMe, the mixt. satd. with CO2 and dild. with H2O satd. with CO2, the mixt. satd. with CO2 and extd. with Et2O, the ext. shaken with aq. NaHCO3 (the alk. ext. combined with the aq. phase), the Et2O ext. exhaustively extd. with ice-cold 0.5% KOH (the alk. ext. satd. with CO2 to give 283 mg. pure V), and the Et2O ext. evapd. gave a trace of IV and Me2CHCH2CO2Me. The aq. phase acidified to Congo red and extd. 2 hrs. with Et2O, the ext. worked up, and the product distd. in high vacuum yielded 71 mg. IV, ***purified*** by ***chromatography*** in 1:1 C6H6-petr. ether over 3 g. neutral Al2O3 and recrystd. from C5H12 and C6H6-C5H12. II (25 mg.) boiled 2.75 hrs. in 2 ml. N NaOMe and the mixt. worked up as above produced a 0.5% KOH ext. yielding V, and a neutral fraction giving IV. IV (39.8 mg.) treated with 3 ml. boiling N NaOMe yielded 11.4 mg. V from the phenolic reaction product. V was converted into the acetate, m. 123.5-4.5.degree. (from Me2CO-H2O and MeOH-H2O); Me ether (Va), m. 107.5-8.5.degree. (from Et2O-petr. ether), no Gibbs color reaction; 2,4-dinitrophenylhydrazine deriv., m. 195.5-6.5.degree. (decompn.), .lambda. (max.) 251, 299, 344, (shoulder) 430, (min.) 224, 276, 318 (log .epsilon. 4.50, 4.25, 4.27, 3.38, 4.13, 4.11, 4.16). V (50 mg.) kept 18 hrs. at 10.degree. in 1.6 ml. 5% aq. KOH, the soln. satd. with CO2, acidified with AcOH, and filtered, and the ppt. crystd. from Me2CO-petr. ether and Me2CO (or C6H6) gave a compd. m. above 310.degree., blue-green Gibbs test. V (50.00 mg.) in 5 ml. AcOH hydrogenated with 3.04 moles H in 5.5 hrs. at 17.degree./716 mm. in the presence of 15.5 mg. 30% Pd-norite catalyst, the mixt. filtered, the filtrate evapd., the residue kept overnight in excess 2.5% KOH in dil. MeOH, the with H2O, the MeOH evapd. in vacuo, the aq. soln. acidified to Congo red and extd. with Et2O, the ext. worked up, the product distd. at 130-40.degree./0.02 mm., and the cryst. portion of the distillate crystd. from dil. MeOH gave the known hexahydroorselone, m. 98.degree.. V (30 mg.) in a little abs. CHCl3 ozonized with 1.7 l. 1% O3 in O at 0.degree., the CHCl3 evapd. in vacuo, the residue treated with dil. aq. NaCl, the soln. distd. at 100-10.degree. in N into dil. p-O2NC6H4NHNH2.HCl, the ppt. (4 mg.) sublimed at 130.degree. in high vacuum, and the sublimate recrystd. from dil. alc. gave acetone p-nitrophenylhydrazone, m. 144-5.degree.. The remaining distillate steam-distd. gave 8 mg. needles, sublimed at 65-70.degree./0.02 mm. and crystd. from dil. Me2CO to give resorcinol-2,4-dialdehyde, m. 128.0-8.5.degree.. V (10 mg.) ozonized in CHCl3 at -15.degree. or -80.degree., the CHCl3 evapd. and the residue steam-distd. (N atm.), the ***acid*** distillate made alk. with a few drops of aq. KOH and paper-***chromatographed*** in BuOH-H2O-NH2Et gave, in both expts., spots corresponding to AcOH and Me2C(OMe)CO2H. Oroselone (VI) (50 mg.) in 2 ml. CHCl3 and 1 ml. AcOH ozonized at 0.degree. with 3 l. 2% O3-O, the CHCl3 evapd. at 20.degree. in vacuo, the residue steam-distd., the distillate treated with p-O2NC6H4NHNH2, and the ppt. sublimed gave formaldehyde p-nitrophenylhydrazone, m. 180-1.degree. (from dil. alc.). V (20 mg.) in 5 ml. alc. illuminated 6 hrs. with unfiltered ultraviolet light, the soln. evapd. in vacuo and the product freed from small amts. of phenolic by-products gave IX for which an .alpha.-pyrone ring structure was proposed. I (120 mg.) heated 4 hrs. at 100.degree. with 5 ml. N NaOMe, the soln. treated portionwise at 100.degree. in 45 min. with 1.2 ml. Me2SO4 in 15 ml. NaOMe under const. alk. conditions, kept 30 min. at 100.degree., cooled, ***neutralized*** at 0.degree. with AcOH, and evapd. at 30.degree. in vacuo, the residue taken up in H2O and extd. with Et2O, the washed and dried ext. evapd., the residue ***chromatographed*** over 1.3 g. neutral Al2O3 and eluted with 3:1

petr. ether -C6H6, and the product crystd. from Et2O-petr. ether gave Va. I (400 mg.) in 5 ml. pure dioxane stirred with 8 ml. 5% aq. NaOH, the soln. kept 20 hrs. at 20.degree. and acidified to weak Congo red, the ***acid*** soln. kept at 0.degree. several days and filtered, and the crude product treated with Norit in Me2CO and recrystd. repeatedly from Me2CO-H2O and Me2CO-Et2O gave an amorphous, optically inactive bimol. compd., C28H22O7, .lambda. (max.) 254, 302, (min.) 233, 279 m.mu. (log..epsilon. 4.67, 4.33, 4.37, 4.12). I (200 mg.) in 6 ml. AcOH hydrogenated 18 hrs. with 1.9 moles H in the presence of 170 mg. PdO2, the soln. evapd. at 40.degree. in vacuo, the product, [.alpha.]D15 37.5.degree. (AcOH), heated 3.5 hrs. at 100.degree. with 5 ml. 5% KOH, acidified, and extd. with Et2O, the ext. washed with aq. NaCl and evapd., the residue distd. at 160-80.degree./0.05 mm., and the oily residue recrystd. from Et2O-petr. ether yielded 70 mg. VII, m. 112-13.degree., [.alpha.]58919 86.7 .+-. 2.degree., [.alpha.]54622 106.2 .+-. 2.degree., [.alpha.]43621 129.1 .+-. 6.degree. (c 0.6504, MeOH), [.alpha.]58919 66.5 .+-. 2.degree., [.alpha.]54620 82.2 .+-. 2.degree., [.alpha.]43621 100.6 .+-. 6.degree. (c 0.620, CHCl3), .lambda. (max.) 280, 289, (min.) 261, 285 m.mu. (log .epsilon. 3.30, 3.32, 2.88, 3.31); acetate, [.alpha.]D20 58.5 .+-. 1.5.degree. (c 0.729, CHCl3). VII (17 mg.) in 3 ml. H2O distd. slowly (N atm.) with 0.5 ml. mixt. (6 g. K2Cr2O7 and 8 g. H2SO4 in 27 ml. H2O) into dil. aq. p-O2NC6H4NHNH2.HCl, the ppt. (5 mg.) sublimed, the sublimate crystd. from dil. alc. and Et2O-petr. ether gave acetone p-nitrophenylhydrazone, m. 146-8.degree.. I (5 g.) in 50 ml. Et2O added dropwise in 2-3 hrs. at 20.degree. to vigorously agitated 2.5 g. LiAlH4 in 200 ml. abs. Et2O, the mixt. stirred 4 hrs., kept overnight, treated cautiously with EtOAc-Et2O, ***neutralized*** with cold N HCl, and extd. with CH2Cl2, the dried ext. evapd. in vacuo, the residue taken up in a little MeOH and kept 12 hrs. with excess CH2N2 in Et2O, the mixt. worked up, the residue extd. with C5H12, and the insol. product ***chromatographed*** over 100 g. Al2O3 (contg. 10% H2O), eluted with 400 ml. C6H6 and 1200 ml. 20:1 and 10:1 C6H6-CH2Cl2 and the product crystd. repeatedly from Et2O gave 2-(1-methyl-1-hydroxyethyl)-2,3-dihydro-4-methoxy-5-[2-(hydroxymethyl)vinyl] benzofuran (VIII), C15H20O4, m. 95-6.degree., [.alpha.]D21 57.4 .+-. 2.degree. (c 0.714, CHCl3), .lambda. (max.) 217, 261, (min.) 238 m.mu. (log .epsilon. 4.39, 4.17, 3.81). Further elution with CH2Cl2-MeOH gave the amorphous 3-HO deriv. (IX) of VIII, [.alpha.]D17 59 .+-. 3.degree. (c 1.00, MeOH), .lambda. (max.) 260, (min.) 244 m.mu. (log .epsilon. 3.8, 3.63). The formation of VIII and IX was only possible if I had the proposed formula. I, [.alpha.]58921 102.3 .+-. 2.degree., [.alpha.]54622 129.0 .+-. 2.degree., [.alpha.]43622 161.4 .+-. 6.degree. (c 0.5575, MeOH), [.alpha.]58921 60.0 .+-. 1.degree., [.alpha.]54621 73.9 .+-. 1.degree., [.alpha.]43621 86.3 .+-. 3.degree. (c 1.024, CHCl3). In AcOH the rotation of I, [.alpha.]D20 88 .+-. 1.degree. (c 1.145), remained const. during several days, but I (c 0.465, N p-MeC6H4SO3H in MeOH) at 20 .+-. 2.degree. had .alpha.D 0.51, 0.66, 0.64, 0.56, 0.04.degree. in 1, 17, 41, 89, and 1152 hrs., resp., and had decompd. to a mixt. of VI and a substance with the ultraviolet absorption spectrum of IV. I also racemized in N HCl in MeOH with formation of VI which was itself partially changed under these conditions. Et2O ext. (4.5 g., from roots of Athamanta oroselinum) ***chromatographed*** on 225 g. 3:1 ZnCO3-Hyflo, eluted with C5H12 and 3:1 C5H12-C6H6 to remove oils, VI, and I, eluted further with C5H12-C6H6-Et2O, and the product crystd. from Et2O or CH2Cl2 and ***purified*** by high vacuum distn. gave optically inactive oroselol (X), m. 156-7.degree., .lambda. (max.) 251, 301, (min.) 230, 272 m.mu. (log .epsilon. 4.44, 4.04, 4.00, 3.64), oxidized by CrO3 to give Me2CO, no MeO group, no FeCl3 or Gibbs reactions.

X (40 mg.) heated 30 min. at 100.degree. with 1 ml. MeOH and 0.5 ml. concd. HCl, the mixt. dild. with H2O, and the ppt. ***purified*** by high vacuum distn. and crystn. from Et2O and EtOH gave VI, also obtained by refluxing X 2.5 hrs. with NaOAc-Ac2O. X (10 mg.) in 3 ml. 0.9N HCl in abs. MeOH kept 24 hrs. at 20.degree., the mixt. poured into excess aq. NaHCO3 and extd. with CH2Cl2-petr. ether, the ext. evapd., the residue distd. at 140-50.degree. in high vacuum, the crude product (m. 107-10.degree.) taken up in C6H6 and filtered through ZnCO3-Hyflo, the filtrate evapd., and the residue crystd. from C6H12 or Et2O gave IV. The transformation of X to IV and VI permitted the assignment of a coumarin formulation. The coumarin-coumaric ester reversible rearrangement was investigated. Umbelliferone Me ether (XI) (800 mg.) refluxed 3.5 hrs. with 40 ml. N NaOMe, the mixt. satd. with CO2, dild. with H2O, again satd. with CO2, evapd. in vacuo at 30.degree., and extd. with Et2O, the Et2O ext. shaken out with ice-cold 0.5% aq. KOH, the aq. ext. acidified and, after long standing, filtered, and the residue (540 mg.) recrystd. from C6H6-petr. ether gave Me trans-2-hydroxy-4-methoxycinnamate (XII), m. 144.5-5.0.degree., yellow soln. in NaOH, blue-green Gibbs test, not converted to XI on brief distn. at normal pressure; free ***acid*** , m. 195-8.degree. (from H2O). XI (500 mg.) kept 20-24 hrs. at 4-6.degree., the mixt. satd. with CO2, dild. with H2O in a strong stream of CO2, evapd. in vacuo at 20-30.degree., and extd. with Et2O, and the Et2O extd. with 0.5% aq. KOH, the alk. ext. acidified and extd. with Et2O, and the product on evapn. recrystd. from Et2O-petr. ether and dil. MeOH gave 380-400 mg. Me .beta.-methoxy-.beta.-(2-hydroxy-4-methoxyphenyl)propionate (XIII), m. 83.5-4.5.degree., colorless soln. in NaOH, blue Gibbs test, converted by distn. at 160.degree./14 mm. to XI. XIII (60 mg.) heated 15 min. at 100.degree. with 0.3 ml. AcOH, the mixt. evapd. in vacuo and worked up as above gave 2.2 mg. crude XI and 50 mg. phenolic material ***purified*** by filtration in Et2O through neutral Al2O3 and crystn. of the product from C6H6-petr. ether to give XII. XIII (200 mg.) methylated 10 hrs. at 60-5.degree. with K2CO3 and MeI in Me2CO, the mixt. worked up, and the 178 mg. cryst. neutral product recrystd. from Et2O-petr. ether gave Me .beta.-methoxy-.beta.-(2,4-dimethoxyphenyl) propionate (XIIIa), m. 52.5-5.0.degree., .lambda. (max.) 228, 276, (min.) 249 m.mu. (log .epsilon. 3.94, 3.47, 2.54) (similar to that of XIII), distd. unchanged at 180-200.degree./14 mm. XIIIa (65 mg.) heated 3 hrs. at 100.degree. with 3 ml. N NaOMe, the mixt. worked up, and the crude product (m. 83.5-5.0.degree.) distd. at 120.degree./0.03 mm. and recrystd. from Et2O-petr. ether gave the known Me trans-2,4-dimethoxycinnamate, m. 86.5-7.0.degree.. XI (100 mg.) was heated 3 hrs. at 85 .+-. 2.degree. (anhyd. atm.) with 5 ml. N NaOMe, the cooled mixt. ***neutralized*** with AcOH, evapd. at 20.degree. in vacuo, dild. with H2O, and extd. with Et2O, the Et2O ext. shaken with aq. NaHCO3 (ext. A), and exhaustively extd. with ice-cold 0.5% KOH (ext. B). Acidification of ext. A yielded 18.9 mg. XI. Ext. B satd. with CO2 and worked up gave 70.3 mg. XII. Evapn. of the original Et2O ext. gave 14.2 mg. XI. By similar treatment, 100 mg. XII produced 11.2 mg. XI and 90.6 mg. XII; 100 mg. XIII gave 22.7 mg. XI and 46 mg. XII. .beta.-Methoxymeliotic esters of type XIII constituted the intermediate products in the alkylate catalyzed reversible coumarin (or coumarinic ester)-coumaric ester rearrangement. I had a 100 times stronger coronary dilating activity than aminophyllin and a 10-fold weaker spasmolytic activity on the ***isolated*** intestine than ***papaverine*** . In the mouse the toxicity of I was equiv. to that of khellin and ***papaverine*** .

L10 ANSWER 10 OF 13 CAPLUS

AN 1957:39198 CAPLUS
DN 51:39198
OREF 51:7344i,7345a-i,7346a-i,7347a-i,7348a-i,7349a-b
TI Synthesis of alicyclic derivatives structurally related to morphine. II
AU Winternitz, F.; Antia, N. J.; Tumlirova, M.; Lachazette, R.
CS Univ. Montpellier
SO Bull. soc. chim. France (1956) 1817-28
DT Journal
LA Unavailable
CC 10 (Organic Chemistry)
AB cf. C.A. 47, 4295e. The importance of the O bridge in ***morphine*** analogs for physiol. activity may be relative to the completeness of the structural analogy. With lack of phenanthrene or isoquinoline components, the necessity for the furan structure for ***morphine*** -like activity may become more evident as shown by the synthesis of such compds. from 2-phenoxycyclohexanone (I). Anhyd. K2CO3 (132 g.), 127 g. 2-chlorocyclohexanone, 90 g. redistd. PhOH, and 150 cc. Me2CO refluxed 6 hrs., cooled and filtered, the filtrate and Me2CO washings evapd., the residue taken up in Et2O, the washed and dried ext. evapd. and the product recrystd. from Et2O-petr. ether gave 100 g. I, m. 63-4.degree.; dinitrophenylhydrazone, m. 145-6.degree. (from alc.). I (5 g.) added portionwise with stirring to 50 cc. H3PO4, the mixt. heated 2 hrs. at 100.degree., cooled and poured onto cracked ice, the mixt. extd. with Et2O, the washed and dried ext. evapd. and the residue distd. in vacuo gave 3.3 g. tetrahydrodibenzofuran (II), b0.02 100-10.degree.; picrate, m. 97-8.degree. (from alc.), converted by ***chromatography*** in C6H6 over Al2O3, to a compd., C12H12O, b0.02 90-2.degree. II (2 g.) in 25 cc. CCl4 brominated with 2 g. N-bromosuccinimide under 120-w. illumination, the mixt. cooled to 0.degree. and filtered, the filtrate evapd. in vacuo and the residue (3 g.) refluxed 8 hrs. with 2 g. anhyd. K2CO3 in 20 cc. dioxane, the mixt. cooled and taken up in H2O, the soln. extd. with Et2O and the residue on evapn. distd. in vacuo gave 0.5 g. dihydrodibenzofuran (III), b0.02 95-7.degree., .lambda. 250, 280, 286, 296 m.mu. (log .epsilon. 4.08, 3.82, 3.79, 3.40) (picrate, m. 95.0-6.5.degree.), together with viscous oily bromotetrahydrodibenzofuran (IV), b0.02 115-20.degree.. III (0.2 g.) heated 2 hrs. at 300.degree. with 0.2 g. 25% Pd-C and the product extd. with Et2O gave, on standing, cryst. dibenzofuran, m. 82-3.degree. (from alc.); picrate, m. 95-7.degree.. IV (7.7 g.) in 25 cc. anhyd. C6H6 and 20 cc. 30% NHMe2 in C6H6 were kept at room temp. 24 hrs., the mixt. poured onto ice, the C6H6 layer washed with 10% HCl, the washing and the aq. layer made alk. with Na2CO3 and extd. with Et2O, the washed and dried ext. evapd. and the residue distd. in vacuo yielded 71% dimethylamino-1,2,3,4-tetrahydrodibenzofuran (V), b0.04 90-8.degree.; HCl salt, m. 244-6.degree. (from alc.-Et2O); picrate, m. 164-5.degree.. PhSH(4 g.), 5 g. 2-chlorohexanone, and 5 g. K2CO3 in 40 cc. Me2CO refluxed 15 hrs., cooled and taken up in H2O, extd. with Et2O, the washed and dried ext. evapd. and the residue distd. in vacuo yielded 81% 2-(phenylthio)cyelohexanone (VI), b0.04 118-20.degree., m. 53-4.degree. (from Et2O-petr. ether); 2,4-dinitrophenylhydrazone, m. 158-60.degree.. VI (10 g.) in 50 cc. AcOH and 33 cc. Ac2O treated portionwise with 56 cc. 30% H2O, the mixt. heated 2 hrs. at 80.degree. and concd. in vacuo after destruction of excess H2O, the residue taken up in alc., the soln. filtered and evapd. in vacuo, and the residue crystd. from dil. alc. pptd. a small amt. of the sulfone, m. 85-6.degree.. The main product was adipic ***acid*** . VI (5 g.) stirred 3 hrs. with 20 cc. H3PO4, the mixt. heated 3 hrs. at 100.degree. the red soln. poured onto ice and extd. with Et2O, the washed and dried ext. evapd. and the residue distd. in vacuo

gave 4.0 g. 1,2,3,4-tetrahydrodibenzothiophene (VII), b0.04 110-20.degree.; picrate, m. 106-8.degree.. Oxidation of VII with 30% H2O2 in AcOH and Ac2O produced the corresponding sulfone, m. 175-7.degree., reduced by LiAlH4 in anhyd. Et2O and worked up to give VII. II (2.2 g.) in 0.6 g. AcOH and 0.5 g. Ac2O treated portionwise with 0.46 g. SeO2, the mixt. heated 45 min. on a steam bath, the cooled soln. taken up in H2O and extd. with Et2O, the ext. distd. in vacuo gave dibenzofuran, b0.04 80.degree., and 1.1 g. oil, b0.04 125-30.degree., hydrolyzed by boiling 3 hrs. in 10% NaOH to 4-hydroxy-1,2,3,4-tetrahydrodibenzofuran (VIII) (phenylurethan, m. 143-5.degree.), together with an isomeric alc. (phenylurethan, m. 127-35.degree.). Cyclohexanone (35 g.) in 100 cc. PhMe, 3 g. VIII and 5 g. Al(OCHMe2)3 refluxed 10 hrs., the mixt. steam distd., the residue extd. with Et2O, the washed and dried ext. evapd. and the residue crystd. from Et2O-petr. ether gave 2.2 g. 4-oxo-1,2,3,4-tetrahydrodibenzofuran (IX), m. 63-65.degree.; oxime, m. 182-3.degree. (from 95% alc.); 2,4-dinitrophenylhydrazone, m. 223-5.degree., .lambda. 394 m.mu.. IX (0.5 g.) in 25 cc. CCl4 and 0.450 g. N-bromosuccinimide refluxed 1 hr., the mixt. cooled and filtered, the filtrate evapd. in vacuo at 40.degree., the oily residue refluxed 10 hrs. with 10 cc. PhNMe2, the mixt. extd. with Et2O, the ext. washed with dil. HCl, H2O and 10% NaOH, the alk. ext. acidified and extd. with Et2O, the dried ext. evapd. and the residue recrystd. from petr. ether gave 4-hydroxydibenzofuran, m. 98-9.degree.. II (16 g.) in 20 g. AcOH and 12 g. CrO3 in 28 cc. AcOH stirred 12 hrs. at 25-30.degree., the mixt. decompd. and extd. with C6H6, the ext. washed with satd. aq. Na2CO3 and H2O, dried, evapd. in vacuo and the residue distd. gave 6 g. II and 8 g. 1a,4a-epoxy-1,2,3,4-tetrahydrodibenzofuran (X), b0.05 125-30.degree., m. 108-10.degree.. X (2 g.) refluxed 1 hr. with 10% NaOH, the mixt. extd. with Et2O and the residue acidified yielded o-HOC6H4CO(CH2)4CO2H, m. 91-2.degree.; semicarbazone, m. 182-4.degree.; oxime, m. 125-7.degree.. II (4 g.) added to 2.9 g. BzO2H in 35 cm. CHCl3, after 2 hrs. the mixt. taken up in H2O, the org. layer washed with dil. NaOH and H2O, the dried ext. evapd., and the residue distd. gave a crude product, b0.07 125-30.degree., m. 62-5.degree., ***purified*** by ***chromatography*** in Et2O to 1a,4a-dihydroxy-1,2,3,4-tetrahydrodibenzofuran, m. 70-2.degree.. I (25 g.) and 18 g. BrCH2CO2Et in 200 cc. C6H6-PhMe added portionwise to 9 g. Zn and 2 crystals of iodine in 150 cc. C6H6-PhMe with brief warming to initiate the reaction the mixt. refluxed 3 hrs. with stirring, cooled, and decompd. by addn. of 50 cc. AcOH and 60 cc. MeOH, the clear soln. dild. with H2O, the aq. layer extd. with C6H6, the dried ext. evapd. in vacuo and distd. gave 4 g. I and 30 g. product (XI), b0.01 120-50.degree.. X1 (6 g.) refluxed 5 hrs. with 4.5 g. KOH in 25 cc. H2O and 25 cc. alc., the mixt. concd. in vacuo, dild. with H2O and extd. with Et2O, acidified and again extd. with Et2O, the washed and dried Et2O ext. evapd., the clear oily residue taken up in alc., the soln. satd. 15 min. at 0.degree. with dry HCl and kept 12 hrs. at room temp., evapd. in vacuo, the residue taken up in H2O, the soln. extd. with Et2O, the ext. washed with dil. NaOH and H2O, evapd. and the residue distd. gave an oily mixt. of ester and lactone, b0.02 130-40.degree., sapond. by alc. KOH to give 2.4 g. ***acid*** product (XII); S-benzylisothiuronium salt, m. 125-7.degree.; amide, m. 130-2.degree.. Attempts to cyclize XII with concd. H2SO4 or H3PO4-HCO2H gave an ***acid*** [S-benzyl-thiuronium salt, m. 156-8.degree., .lambda. 273, 279 m.mu. (log .epsilon. 2.74, 2.74)], showing no change on cyclization and suggesting isomerization by shift of the double bond. I (5 g.), 2.7 g. NCCH2-CO2Et, 3,6 g. AcOH, and 1.8 g. anhyd. NH4OAc refluxed 18 hrs. in 45 cc. anhyd. C6H6, the cooled mixt. extd. with Et2O, the washed and dried ext. evapd., and the residue distd.

in vacuo gave 5.5 g. distillate, b0.03 130-50.degree., redistd. to yield Et 2-phenoxycyclohexylidene-.alpha.-cyanoacetate (XIII), b0.02 130-40.degree.. Hydrolysis of XIII with 10% Na2CO3 caused no change after 7 hrs. refluxing, but hydrolysis by heating 10 hrs. with 20% Na2CO3 in dioxane regenerated I. XIII (2.6 g.) and 4.1 g. NaOH heated 6 hrs. in 30 cc. 95% alc., the reaction products sepd. into ***acid*** and neutral fractions and the neutral fraction ***chromatographed*** over Al2O3 and eluted with 1:1 C6H6-petr. ether gave 1.1 g. trans-2-phenoxycyclohexanol (XIV), m. 81-2.degree.; p-toluenesulfonate, m. 116-17.degree.. The infrared spectrum of XIV shows a distinct C-OH band. I (3 g.) in 30 cc. Et2O refluxed 30 min. with 0.4 g. LiAlH4 in Et2O, the mixt. decompd. with excess NH4OH, the Et2O layer washed, dried and evapd., and the residue fractionally recrystd. from Et2O-petr. ether gave cis-2-phenoxycydohexanol (XIVa), m. 80-1.degree., and a small yield of impure XIV. Attempts to condense I with MeNO2 were unsuccessful though the CO group seems particularly reactive to KCN. I (8 g.) in 10 cc. alc. and 16 g. NaHSO3 in 30 cc. H2O heated on a steam bath, the soln. boiled with 2.8 g. KCN and filtered hot, the filtrate kept 17 hrs. at 0.degree. and dild. with H2O, the soln. extd. with Et2O, the washed and dried ext. evapd., the residue (6 g.) crystd. from Et2O-petr. ether, the crude product (m. 100-5.degree.) ***chromatographed*** over Al2O3 and eluted with 3:2 and 4:1 C6H6-petr. ether yielded 20% cyanohydrin (XV), m. 108-11.degree.. Further elution with C6H6 gave 80% cyanohydrin (XVa), m. 78-80.degree.. Dropwise addn. of 25 cc. AcOH to 8 g. I and 16 g. KCN in 80 cc. alc., 4 hrs. ***isolation*** at room temp. and refluxing 1 hr., decompn. with H2O and extn. with Et2O, evapn. of the washed and dried ext., distn. of the residue and crystn. of the distillate from Et2O-petr. ether gave 4.8 g. XVa and 1 g. XV. The presence of the HO group was shown by Zerevitinov detn. and by regeneration of I with NaOMe according to Zemplen or with ammoniacal AgNO3 by the method of Wohl. Attempts to cyclize XV, XVa, and the cyanohydrin from 2-(2-methoxyphenoxy)cyclohexanone failed to give the expected tetrahydrodibenzofuran derivs. XV (1.2 g.) in 60 cc. Et2O added to 0.3 g. LiAlH4 in 30 cc. Et2O at -10.degree., the mixt. refluxed 30 min. and stirred 2 hrs. at room temp., decompd. by addn. of 150 cc. 20% H2SO4, the neutral products extd. with Et2O, the aq. phase made alk. with NH4OH and extd. with CHCl3, the ext. dried over Na2CO3, evapd. in vacuo, and the residue crystd. from Et2O-petr. ether gave 1 g. 1-aminoethyl-2-phenoxycyclohexanol, m. 106-8.degree.. Similarly, 1 g. XVa yielded 0.8 g. isomeric 1-aminoethyl-2-phenoxycyclohexanol, m. 60-1.5.degree.. A mixt. of XV and XVa (10 g.) in 60 cc. 95% alc. and 20 cc. AcOH was hydrogenated at 46.degree./100 kg. in the presence of 2 g. Raney Ni, the mixt. filtered, the filtrate concd. in vacuo, the residue taken up in H2O and extd. with Et2O, the aq. phase made alk. with Na2CO3 and extd. with CHCl3, and the residue distd. to give 6 g. amine, b0.05 110-18.degree., converted by treatment with 10 g. 98% HCO2H and 20 cc. 30% HCHO 2 hrs. at 100.degree., concg. the cooled mixt. in vacuo, taking up the residue in H2O, making alk. with Na2CO3, extg. with CHCl3, evapg. the ext. and distg. the residue to 1-dimethylaminoethyl-2-phenoxy-cyclohexanol (XVI), b0.02 110-20.degree.; picrate, m. 135-7.degree.; HCl salt, m. 206-8.degree.. Zerevitinov detn. showed the dimethylation to have taken place without dehydration. A mixt. of XV and XVa (5 g.) in 30 cc. 95% alc. hydrogenated at 60.degree./100 kg. in the presence of 1 g. Raney Ni gave 2 g. 1-aminoethyl-2-phenoxy-cyclohexane (picrate, m. 132-4.degree.), dimethylated to 85% 1-dimethylaminoethyl-2-phenoxycydohexane, b0.1 104-6.degree.; picrate, m. 161-3.degree.; HCl salt, m. 171-2.degree.. Conversion of 2-(2-methoxyphenoxy)cyclohexanone by the AcOH method gave

only one isomer of 1-cyano-2-(2-methoxyphenoxy)cyclohexanol, m. 128-30.degree., reduced to 1-aminoethyl-2-(2-methoxyphenoxy)cyclohexanol, m. 73-5.degree.. Various attempts to cyclize XVI failed to produce dibenzofuran derivs. The 2-aryloxycyclohexanones give good yields of Mannich bases resistant to ***acid*** hydrolysis in which the alkylaminoalkyl group is at position 6. These bases have analgesic properties and to press the ***morphine*** structure analogy more closely have been cyclized to tetrahydrodibenzofuran derivs. I (100 g.), 50 g. NHMe2.HCl, and 25 g. paraformaldehyde in 100 cc. abs. alc. contg. 1 cc. HCl refluxed 3 hrs. and a few min. more after addn. of 100 cc. abs. alc. gave 90 g. pure 6-dimethylaminomethyl-2-phenoxycyclohexanone-HCl, m. 177-8.degree.; free base (XVII), m. 78-9.degree.; picrate, m. 143-4.degree.. Similarly were prepd. 6-piperidinomethyl-2-phenoxycyclohexanone (XVIIa), m. 82-4.degree. (MeI salt, m. 152-4.degree.), 6-morpholino-methyl-2-phenoxycyclohexanone (XIIb), m. 115-16.degree. (from CHCl3-Et2O), and 6-dimethylaminomethyl-2-(2-methoxyphenoxy)cyclohexanone (XVIIc), m. 69-71.degree.; HCl salt, m. 156-8.degree.. XVII (3 g.) in 60 cc. Et2O added dropwise at 0.degree. to 0.5 g. LiAlH4 in 60 cc. Et2O, the mixt. refluxed 2 hrs., decompd. at -10.degree. with 90 cc. 15% KOH, the aq. phase extd. with CHCl3 and the ext. added to the org. phase, the mixt. washed in a min. of H2O, dried and evapd. gave cryst. 6-dimethylaminomethyl-2-phenoxycyclohexanol (XVIII), m. 95-6.degree.; HCl salt, m. 216-18.degree. (from Et2O). XVII.HCl (3.2 g.) and 2.2 g. Al(OCHMe2)s in 30 cc. Me2CHOH refluxed 4 hrs., the mixt. evapd. in vacuo, the residue decompd. by heating with 30 cc. 10N NaOH at 100.degree., the oily residue extd. with CHCl3, and the washed and dried ext. evapd. yielded an isomeric cryst. amino alc., m. 96-7.degree.. Distn. of the mother liquors produced 1 g. oil, b0.02 120-45.degree. (HCl salt, m. 174-6.degree.), and 0.5 g. XVIII, b0.02 145-50.degree.. Similarly, XVIIc was reduced by LiAlH4 to 6-dimethylaminomethyl-2-(2-methoxyphenoxy)cyclohexanol, b0.03 150-60.degree.; HCl salt, m. 164-6.degree. (from Et2O). XVII (4 g.) in 6 cc. HCO2H and 6 cc. H3PO4 at room temp. 20 hrs., heated 3 hrs. at 130.degree., the mixt. poured onto ice and, after preliminary ext. with Et2O, made strongly alk. with NH4OH and carefully extd. with CHCl3, the washed and dried ext. evapd. in vacuo, the residue distd., the distillate taken up in Et2O, the soln. washed with 10% NaOH and H2O, dried and distd. in vacuo gave colorless oily 1-dimethylaminomethyl-1,2,3,4-tetrahydrodibenzofuran (XIX), b0.05 87-90.degree.; picrate, m. 156-8.degree.; HCl salt, m. 225-9.degree. (from Et2O). XIX has .lambda. 254, 280, 287 m.mu. (log .epsilon. 4.06, 3.56, 3.50) in close agreement with II, .lambda. 253, 279, 286 m.mu. (log .epsilon. 4.11, 3.66, 3.65) and in contrast to XVII, .lambda. 272, 278 m.mu. (log .epsilon. 3.18, 3.09). Treatment of the Mannich bases XVII, XVIIa, and XVIIb with PhMgBr and XVII with p-MeOC6H4MgBr and working up gave the corresponding substituted cyclohexanols, 1,2,6-Ph(PhO)(R'R''NCH2)C6H8OH (NR'R'' and m.p. given): NMe2, 98-110.degree. [HCl salt, m. 244-5.degree. (decompn.)]; piperidino, 146-8.degree.; morpholino, 167-9.degree. (HCl salt, m. 98-100.degree.). 2,1,6-PhO(p-MeOC6H4)NMe2CH2C6H8OH b0.03 170.degree., m. 110-13.degree.. VI (6 g.), 3.4 g. morpholine-HCl, and 1.3 g. paraformaldehyde refluxed 20 hrs. in 40 cc. alc., the mixt. treated with 1 g. paraformaldehyde and 0.5 g. concd. HCl and refluxed 3 hrs., and the product worked up gave 2-phenylthio-6-morpholinocyclohexanone (XX), m. 93-5.degree. (picrate, m. 135-7.degree.), stable to 3 hrs. heating at 80.degree. in 10% H2SO4. VI (6 g.) and 2.4 g. morpholine treated at 0.degree. by dropwise addn. of 2.5 g. 30% HCHO in 25 cc. MeOH, the mixt. kept 1 hr. at room temp., refluxed 7 hrs. and worked up by the method of Mannich and Strauss (C.A. 38, 14848)

gave a base (XXI), m. 99-102.degree.; picrate, m. 150-2.degree. (decompn.); HCl salt, m. 160-3.degree.. Hydrolysis of XXI with dil. H2SO4 gave the original VI and it is suggested that XXI is produced by O-alkylation. A study has been made of the stereoisomerism of the pharmacodynamically important .beta.-aryloxycyclohexylamines prepd. by the methods of Rericha (C.A. 45, 576b), Hayes and Peterson (C.A. 47, 569a), and Kopp (C.A. 49, 9540i). PhOH (4.7 g.) and 4.8 g. 1,2-cyclo-hexeneimine heated 12 hrs. at 100.degree., the mixt. taken up in Et2O, the washed and dried ext. evapd. and the residue distd. gave 60% trans-1-amino-2-phenoxycyclohexane (XXII), b0.06 117.degree.; picrate, 160-3.degree. (from C6H6); HCl salt, m. 213-15.degree. (from Et2O). XXII (2.5 g.), 1.7 g. EtBr, and 1.5 g. K2CO3 in 30 cc. alc. refluxed 12 hrs., the cold mixt. dild. with H2O, made strongly alk. with NaOH and extd. with Et2O, the ext. refluxed 4 hrs. with EtBr and K2CO3, the mixt. reextd. with Et2O, the ext. evapd., and the residue distd. gave trans-1-diethylamino-2-phenoxycyclohexane (XXIIa), b0.05 120-8.degree.; picrate, m. 112-15.degree. (from alc.). PhONa (from 4.5 g. PhOH and 1.1 g. Na) in 40 cc. abs. alc. and 9 g. cis-2-chloro-1-diethylaminocyclohexane refluxed 6 hrs. and evapd., the residue in 10% HCl freed from neutral products by Et2O extn. and made alk. with powd. Na2CO3, the alk. soln. extd. with Et2O, the washed and dried ext. evapd. and the residue distd. in vacuo yielded 23% XXIIa; perchlorate, m. 122-4.degree. (from Et2O). XXII (3 g.), 4.5 g. HCO2H, and 9 g. 30% HCHO heated 2 hrs. at 80.degree. and 1 hr. at 120.degree., the mixt. concd. in vacuo and the residue taken up in NaOH, the base extd. with CHCl3, the ext. evapd. and the residue distd. in vacuo gave trans-1-dimethylamino-2-phenoxycyclohexane (XXIIb), b0.04 100-5.degree.; picrate, m. 155-7.degree.. PhOH (6.5 g.) treated with 1.6 g. Na in 15 cc. alc. and 50 cc. PhMe and 13 g. cis-2-chloro-1-dimethylaminocyclohexane, refluxed 6 hrs., and the product ***isolated*** as before gave 1 g. XXIIb. I (10 g.), 10 g. HONH2.HCl, and 10 cc. pyridine in 80 cc. alc. refluxed 12 hrs., the mixt. evapd. in vacuo, the residue taken up in H2O, the soln. extd. with Et2O, the washed and dried ext. evapd., and the residue distd. gave 7.8 g. 2-phenoxycyclohexanone oxime (XXIII), b0.04 110-35.degree., m. 82.0-4.5.degree.. XXIII (2.5 g.) in 25 cc. Et2O added dropwise to 0.64 g. LiAlH4 in Et2O, the complex refluxed 2 hrs. and decompd. at 0.degree. with 100 cc. 30% KOH, the CHCl3 washings of the aq. phase and the Et2O layer combined, washed, dried and evapd., and the residue distd. in vacuo yielded 78% cis-1-amino-2-phenoxycyclohexane (XXIV), b0.02 110-20.degree.; picrate, m. 173-6.degree. (from alc.); HCl salt, m. 246-8.degree. (decompn.).

XXIII (3.8 g.) in 60 cc. alc. reduced 12 hrs. in the presence of 1 g. Raney Ni, the mixt. filtered and the filtrate, acidified with HCl, concd. in vacuo, the residual salt taken up in H2O and extd. with Et2O, the aq. phase made alk. with NH4OH and extd. with Et2O, the ext. evapd. and the residue distd. gave XXIV, also obtained by heating 10 g. I and 20 g. HCONH2 4 hrs. at 180.degree. in a sealed tube and working up the product or by heating 10 g. I with 20 g. HCONH2 and 2.4 g. HCO2H 12 hrs. at 130.degree.. XXIV (5.5 g.), 8.5 g. 98% HCO2H, and 17.5 g. 30% HCHO heated 2 hrs. at 80.degree. and 2 hrs. at 130.degree., the base extd. with dil. HCl to sep. the required tertiary amine from the acetylated secondary base, the ***acid*** phase ***neutralized*** and extd. with Et2O, the ext. washed, dried and evapd., and the residue distd. gave 3 g. pure cis-1-dimethylamino-2-phenoxycyclohexane (XXIVa), b0.04 105-8.degree.; picrate, m. 170-3.degree.. XXIVa was similarly prepd. by the Leuckart-Wallach reaction by heating 10 g. I, 15.2 g. HCONMe2, and 2.4 g. HCO2H 16 hrs. at 140.degree.. XXIV (1.6 g.), 3g. EtI in 15 cc. alc., and

0.5 g. KOH in 10 cc. H2O refluxed 20 hrs., the product taken up in H2O, the base extd. with Et2O and distd. gave 1 g. cis-1-ethylamino-2-phenoxycyclohexane, b0.04 115-20.degree.; picrate, m. 151-3.degree.. XXIV (9.5 g.) and 25 g. p-MeC6H4-SO3Et in 100 cc. PhNO2 heated 10 min. at 220.degree., the cold soln. taken up in 20% HCl, the mixt. steam-distd. and the residual liquid filtered, the filtrate made alk. with Na2CO3 and extd. with Et2O, the ext. washed, dried and evapd., the residue distd. and the crude residue, b0.05 100-20.degree., ***purified*** through Ac2O gave cis-1-diethylamino-2-phenoxycyclohexane (XXIVb); picrate, m. 135-7.degree. (from alc.); perchlorate, m. 114-16.degree.. XXIV (5 g.), 3.7 g. EtBr, and 3.5 g. anhyd. K2CO3 in 150 cc. abs. alc. refluxed 15 hrs., the mixt. taken up in H2O and made alk. with Na2CO3, extd. with Et2O, the ext. evapd. and the residue again refluxed 15 hrs. with 3.7 g. EtBr and 3.5 g. K2CO3 in 150 cc. alc., the mixt. worked up and the product distd. gave XXIVb, also obtained in 30% yield by heating 5 g. I, 3.8 g. NHEt2, and 3.2. g. HCHO 12 hrs. at 190.degree.. Lespagnol-Mercier tests on cats showed XVII and XVIIb to have 6% ***morphine*** activity, reduced by reduction of the ketones to alcs. or by introduction of MeO group into the aromatic ring. All activity is suppressed by replacement of the bridge O atom by a CH2 group.

L10 ANSWER 11 OF 13 CAPLUS COPYRIGHT 2001 ACS
AN 1950:12644 CAPLUS
DN 44:12644
OREF 44:2533i,2534a-i,2535a-c
TI Aporphine alkaloids. II. The synthesis of 10-oxoaporphines
AU Schlittler, E.; Lindemann, A.
SO Helv. Chim. Acta (1949), 32, 1880-91
DT Journal
LA German
CC 10 (Organic Chemistry)
AB cf. C.A. 42, 7302b. The several reported syntheses of aporphine alkaloids involve Pschorr's ring closure of an aminobenzyltetrahydroquinoline to the phenanthrene deriv. and the resulting yields are generally low (5-20%). Merck and Co. in 1926 claimed that the yield was increased considerably when the "bridge" C atom was CO instead of CH2. To prove this 2,3,5,6-bis(methylenedioxy)-(I) and 2,3,5,6-tetramethoxy-10-oxoaporphine (II) were synthesized. Piperonal was condensed with hippuric ***acid*** , the resulting azlactone hydrolyzed to 3,4-methylenedioxyphenylpyruvic ***acid*** , heated with 25% NH4OH in an autoclave at 100.degree., giving .beta.-(3,4-methylenedioxyphenyl)-N-(4,5-methylenedioxyphenacetyl)alaninamide, sapond. with NaOH, the corresponding free ***acid*** , m. 178-80.degree. (from EtOH-C6H6), esterified with CH2N2, the Me ester, m. 120-1.degree. (from MeOH) (10 g.), 20 cc. POCl3, and 50 cc. abs. PhMe refluxed 1 hr., the solvent and excess POCl3 removed in vacuo, the dark residue washed with petr. ether 50 cc. and Et2O 50 cc., the last traces of Et2O removed in vacuo, and the residue heated with 40 cc. water until practically all dissolved and filtered; on standing overnight a cryst. phosphate of Me 1-(4,5-methylenedioxybenzyl)-6,7-methylenedioxy-3,4-dihydro-3-isoquinolinecarboxylate, m. 187-9.degree. (from EtOH), sepd. An aq. soln. of the ester was treated with 20 cc. 30% NaOH, heated 1 hr. on the water bath, cooled, the pptd. Na salt filtered, dried in a vacuum desiccator, then rubbed with 50 cc. 20% AcOH, and the amorphous product filtered and dried to yield 1-(4,5-methylenedioxybenzyl)-6,7-methylenedioxy-3-carboxy-3,4 -dihydroisoquinoline (III). This heated dry at 110.degree. until CO2 evolution ceased (about 10 min.) gave

1-(4,5-methylenedioxybenzyl)-6,7-methylenedioxy-3,4-dihydroisoquinoline, m. 88-9.degree. (from EtOH); picrate, m. 219-21.degree.. III (10 g.) with 1 g. Pd on charcoal in 200 cc. decahydronaphthalene refluxed in a CO2 atm. 8 hrs. was both decarboxylated and dehydrogenated; the hot soln., filtered, concd. in vacuo to 100 cc. and cooled slowly, yielded 1-(4,5-methylenedioxybenzyl)-6,7-methylenedioxyisoquinoline (IV), m. 168-70.degree. (from C6H6) (more could be extd. from the mother liquor); methiodide, m. 268-9.degree. (decompn.) (from Me2CO). IV (5 g.) was added with stirring over a 30-min. period to 40 cc. concd. HNO3 at -5.degree., dild. with 250 ml. ice water with constant stirring, the ppt. filtered, washed with water, rubbed with 10 cc. 2 N NH4OH, and the suspension warmed 10 min. on the water bath, filtered, washed, and dried to yield the (2-nitro-4,5-methylenedioxybenzyl) deriv. (V) of IV, m. 237-8.degree. (from Me2CO). V (2 g.) in 10 cc. Ac2O was treated with 3.6 g. finely powd. Na2Cr2O7, carefully heated to boiling, the heat removed as soon as the exothermic reaction set in, the mixt. heated 0.5 hr. longer after the reaction subsided, cooled, dild. with 20 cc. water, made alk. with 30% KOH soln., extd. with CHCl3, and the ext. dried over K2CO3 and concd. in vacuo to give (1-2-nitro-4,5-methylenedioxybenzoyl)-6,7-methylenedioxyisoquinoline (VI), m. 254-5.degree. (from Me2CO or MeCl). The oxidation could also be accomplished with SeO2 in dioxane. VI (1 g.) and 8 cc. MeI were heated in a bomb tube at 120.degree. 5 hrs., cooled, filtered, and the crystals rubbed twice with Et2O and CHCl3 and dried to give VI.MeI (VII), m. 228-30.degree. (decompn.). VII (400 mg.) in 150 cc. EtOH and 3 drops 20% NaOH soln. was hydrogenated at 21.degree. in the presence of 1 g. Raney Ni catalyst; after 5 mols. of H were absorbed, the catalyst was filtered, the filtrate ***neutralized*** with alc. HCl, the pptd. NaCl filtered, the filtrate concd. in vacuo, the residue dissolved in 15 cc. 2 N HCl, made alk. with 30% KOH, extd. with Et2O, the Et2O ext. dried over K2CO3, treated with alc. HCl, the solvent removed in vacuo, the residue dissolved in 8 cc. 2 N H2SO4 and 4 cc. MeOH, cooled in ice, diazotized with freshly prepd. N NaNO2 soln., treated with Cu powder 0.4 g. (freed of oil with EtOH), heated on a water bath until evolution of N ceased (about 0.5 hr.), filtered hot, the MeOH removed in vacuo, the H2SO4 soln. (VIII) (which should not show coupling ability when tested with R salt in alk. medium) extd. with CHCl3, the CHCl3 ext. dried over Na2SO4, concd. in vacuo, the residue (110 mg.) hydrogenated in 10 cc. MeOH in the presence of 100 mg. Raney Ni at 17.degree., the catalyst filtered, the filtrate concd. to dryness, the residue taken up in 20 cc. 2 N HCl, made alk. with 30% KOH soln., extd. with 180 cc. Et2O (the ***purification*** can be repeated), the Et2O ext. washed with water, dried over K2CO3, concd. in vacuo, and the residue treated with HClMeOH to give 50 mg. I.HCl, m. 230-2.degree. (decompn.), (from MeOH). After extg. VIII with CHCl3 it was made alk. with 30% KOH soln. (IX), extd. with Et2O (emulsions), the Et2O ext. taken up in HCl, made alk., and extd. again with Et2O, dried over K2CO3, concd. in vacuo, and the residue converted to the HCl salt as above to yield 10 mg. I.HCl. The alk. soln. IX was ***neutralized*** with HCl, made alk. with Na2CO3, extd. with CHCl3, and the CHCl3 ext. dried over Na2SO4 and concd. in vacuo to yield 50 mg. of a base. ***Papaverine*** nitrated as described by Pschorr [Ber. 37, 1926(1904)] gave nitropapaveraldine which was treated with MeI as for VI above, and the resulting 1-(2-nitro-4,5-dimethoxybenzoyl)-6,7-dimethoxyisoquinoline-MeI, m. 217-18.degree. (decompn.), was carried through the subsequent reactions described above, giving II (***purified*** by ***chromatography*** over Al2O3), m. 163-8.degree.; HCl salt, m. 211-14.degree.. Heating papaveraldine with

MeI in a bomb tube at 115.degree. gave 1-(4,5-dimethoxybenzoyl)-6,7-dimethoxyisoquinoline-MeI, m. 135-8.degree., which was reduced with 2 mols. H and Raney Ni in EtOH to 1-(4,5-dimethoxybenzoyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline, m. 141-2.degree. (from Me2CO-pentane).

L10 ANSWER 12 OF 13 CAPLUS COPYRIGHT 2001 ACS
AN 1948:4731 CAPLUS
DN 42:4731
OREF 42:1023d-i,1024a-i,1025a-b
TI The extraction of opium. Twenty-five years of commercial experience in the treatment of opium
AU Barbier, Andre
SO Ann. pharm. franc. (1947), 5, 121-40
DT Journal
LA Unavailable
CC 17 (Pharmaceuticals, Cosmetics, and Perfumes)
AB The 3 standard processes for the extn. of ***morphine*** from opium are described and discussed: (1) the Merck process, dating back to 1830, is obsolete. (2) The Thiboumery and Mohr process, dating back to about 1835, gives low yields because the lime always retains some ***morphine*** , and possibly also owing to loss of ***morphine*** by oxidation in alk. soln. (3) The Robertson-Gregory process (described in Wurtz, Dictionnaire de chimie pure et appliqu.acte.ee 1868; Lebeau et Courtois, Trait.acte.e de pharmacie chimique 2nd ed., Vol. 2, No. 2 (C. A. 32, 3910.4); Schwyzer, Die Fabrikation der Alkaloide (C.A. 22, 1017)) is apparently quite simple in principle, but involves working with very impure, highly viscous solns. and involves difficulties in the washing of the crystals and in the sepn. and ***purification*** of the alkaloids. A process was developed which gave yields of the order of 95% of the ***morphine*** content as detd. by the Harrison method. It consisted essentially in: (1) extn. of the opium with water and pptn. of total alkaloids from the concd. soln. with Na2CO3; (2) extn. of the total alkaloids with an org. solvent (e.g., benzene, toluene, C2HCl3) which removes secondary alkaloids and leaves crude ***morphine*** in the insol. residue; (3) taking up the crude ***morphine*** in water and tartaric ***acid*** and crystn. of ***morphine*** ***acid*** tartrate; (4) taking up the latter salt in water and pptn. of free ***morphine*** with NH4OH. In step (2), lixiviation with benzene removes 6% more of the ***morphine*** than straight extn.; this is attributed to the fact that in lixiviation the benzene which passes out first is satd. with secondary alkaloids, gums, etc., and ***morphine*** is much more sol. in this satd. soln. than in a dil. benzene soln. In the assay of opium for ***morphine*** , the delicate points are the trituration of the opium with water (which must be carried out until there is obtained a very smooth and homogeneous paste) and subsequent addn. of and trituration with Ca(OH)2. If these operations are not carried out properly, a hard crust of Ca meconate forms, which prevents complete soln. of the ***morphine*** . Water extn. of the opium is effected countercurrently, in 4 stages, the first extn. being carried out at 40-5.degree. and the others at ordinary temp. Before being discarded, the spent opium should be tested for ***morphine*** , and if it contains more than 0.3% of the original ***morphine*** content it should be extd. further. The aq. opium ext. is evapd. in vacuo to a vol. of 100 l. per 100 kg. of opium, treated at 85-90.degree. with dry Na2CO3 till decidedly alk. to phenolphthalein, stirred 1 hr. at 85-90.degree. (if no

longer alk., more Na2CO3 is added), cooled, filtered, and the ppt. of alkaloids is washed with water. Owing to its water-soly., ***codeine*** should remain in soln., but part of it is found in the total alkaloids, which is attributed to the fact that when the alkaloids are pptd. hot they at first come down in oily form and dissolve some ***codeine*** which is retained when the oil solidifies on cooling. The drained total alkaloids need not be dried before solvent extn. unless C2HCl3 is used as solvent; extn. is continued until the solvent contains less than 1% solids. The crude ***morphine*** is dissolved in a quantity of water at 80-5.degree. equal to twice the wt. of opium used; tartaric ***acid*** is added gradually until the soln. is ***acid*** to litmus (formation of neutral ***morphine*** tartrate); the soln. is treated with decolorizing C, filtered under vacuum, and cooled. An amt. of tartaric ***acid*** equal to that used to ***neutralize*** the crude ***morphine*** is added (soln. ***acid*** to methyl orange) to ppt. ***morphine*** ***acid*** tartrate; after stirring 2 hrs. and standing overnight, the ppt. is filtered under vacuum and washed. Two more crops of crystals can be obtained from the filtrate by concn. They are taken up in water at 85.degree.; NH4OH is added to faint acidity to methyl red (formation of the neutral tartrate); the soln. is treated with an active decolorizing C (5-10% on the wt. of moist tartrate), preferably also with 0.30% AcONa, 0.20% NH4 oxalate, and 0.10% Na hydrosulfite. The soln. is filtered; ***morphine*** is pptd. hot by adding NH4OH to alky. to phenolphthalein (excess is avoided), filtered under vacuum, washed, and dried at 80.degree.. The product is hydrated, contains about 2% impurities, and is suitable for the manuf. of ***codeine*** , dionin, and ***heroin*** . A purer ***morphine*** , suitable, e.g., for the manuf. of ***morphine*** -HCl, can be obtained by cooling the filtered decolorized soln. of neutral ***morphine*** and NH4 tartrates, making slightly ***acid*** to methyl orange (HCl is as suitable as, and cheaper than, tartaric ***acid***) to ppt. ***morphine*** ***acid*** tartrate in a high state of purity, which is filtered, washed, and converted into free ***morphine*** . It is essential for economic operation to ext. all waters from the alk. pptn. of ***morphine*** , as they contain up to 0.75 g. ***morphine*** per l. B. accomplishes this by passing the spent water through a ***column*** , countercurrent to BuOH; recovers the BuOH by distn. in the presence of water, and obtains a tarry ***morphine*** residue which is treated with tartaric ***acid*** in the same way as the crude ***morphine*** . The secondary alkaloids are obtained as a tarry residue after evapn. of the benzene used to sep. them from the crude ***morphine*** . Owing to the ease of prepn. of narceine from narcotine, there is no interest in producing the former from opium. The tarry mixt. is treated with water at 85-90.degree.; tartaric ***acid*** is added to neutrality to methyl red; the mixt. is stirred several hrs. to insure complete soln. of ***codeine*** and thebaine; on cooling, narcotine and ***papaverine*** crystallize and are filtered out. The filtrate is concd.; tartaric ***acid*** is added to acidity to methyl orange, and the pptd. thebaine ***acid*** tartrate crystals are filtered out, washed, and ***purified*** by recrystn. from water. The free base can be obtained by hot pptn. (preferably from hydroalc. soln.) with NH4OH or Na2CO3. ***Codeine*** is recovered from the thebaine tartrate mother liquor as described further on. The narcotine- ***papaverine*** mixt. is treated in a cohobator with 3 parts boiling Me Et ketone, the soln. is decolorized with C, and cooled to crystallize narcotine, which is filtered out, washed with Me Et ketone, and ***purified*** by recrystn. from alc.

Papaverine is pptd. as the ***acid*** oxalate and ***purified*** by recrystn. from water. The ***codeine*** is to be found in the filtrate from the total alkaloids ppt. and in the mother liquors from the thebaine tartrate and from the ***morphine*** tartrate. These are always treated separately, but all in the same way by addn. of NaOH to alk. reaction to phenolphthalein, extn. with benzene, distn. of the solvent, taking up with water at 100.degree., and ***purification*** of the crude ***codeine*** as the HCl salt. The extd. alk. waters are acidified to methyl red with Fe-free HCl, heated, alkalinized with Na2CO3 and cooled; the pptd. impure ***morphine*** is filtered out and the filtrate is extd. with BuOH. Synthetic ***codeine*** is practically always prepd. by decompn. of trimethylphenylammonium morphinate, generally by heating in alc. soln. under pressure at 140.degree.. B. obtained a good yield by driving off the alc. and decompg. the dry salt at 85-8.degree. in vacuo. Brief reference is made to the extn. of ***morphine*** from poppy heads and poppy straw. Tests were started in 1938, but were interrupted by the war. Such extn. may be practical under wartime conditions, but would probably be too expensive under ordinary conditions.

L10 ANSWER 13 OF 13 CAPLUS COPYRIGHT 2001 ACS
AN 1947:6054 CAPLUS
DN 41:6054
OREF 41:1221h-i,1222a-i,1223a-f
TI Calabash curare alkaloids. I
AU Karrer, P.; Schmid, H.
CS Univ. Zurich, Switz.
SO Helv. Chim. Acta (1946), 29, 1853-70
DT Journal
LA German
CC 10 (Organic Chemistry)
AB This is an orienting study, in which Hoffmann-LaRoche calabash ***curare*** powder and methods of sepn. were used, which, in their initial stages, were quite similar to those given by Wieland, Pistor, and Bahr (C.A. 35, 5898.2). K. and S. ***isolated*** 4 alkaloids (first as the reineckates, and finally as appropriate salts). They were C-curarine I (I) (also described by W., P., and B), which is the most important alkaloid of calabash- ***curare*** , small amts of "alkaloid A" (II), and "alkaloid B" (III) and appreciable amts. of calebassine (IV). The main steps involved trituration of 200 g. of the calabash powder with 75 cc. H2O, followed by extn. on a shaking machine with 1.2 l. MeOH, and repeating these extns. (using decreasing amts. of H2O and MeOH). The filtered exts. were evapd. in vacuo at 40.degree., yielding 108.7 g. solids, which, in 200 cc. H2O, were treated with an excess of a satd. soln. of reinecke ***acid*** . The resulting mixed reineckates (77 g.) were extd. with 1.05 l. ***purified*** Me2CO which dissolved about 55 g.; this soln. was treated with 5 l. H2O at 70.degree., the resulting ppt. was taken up in 550 cc. Me2CO and repptd. with 2.75 l. H2O at 70.degree., and the operation repeated with 400 cc. Me2CO and 2 l. H2O, resp. The final ppt. of mixed reineckates (V) was 29.8 g. The mother liquors from all these ppts. were combined and evapd. to dryness in vacuo at 35-40.degree., giving a "sol. dried reineckate" fraction of 25.4 g. that was not further studied. The tedious, repeated ***chromatographic*** sepns. of the components of V, using Me2CO and ***columns*** of Brockmann Al2O3, are fully described, and are given in a detail that cannot be abstracted. A bluish-violet zone in the ***column*** , which was eluted by means of Me2CO, and which formed the 1st filtrate of the

initial Al2O3 ***column*** used, consisted largely of pure I reineckate (VI) which, together with another fraction of VI, totalled 4.95 g. To VI (combined fractions) in 60 cc. Me2CO were added 20 cc. H2O and (dropwise) 153 cc. 7.6% hot aq. Ag2SO4. The mother liquors and washings from the resultant ppt. were treated with 33 cc. of a soln. of 0.982 g. BaCl2.2H2O. The mother liquors and washings from the resultant BaSO4 ppt. were combined and evapd. in vacuo, the residue extd. with boiling abs. EtOH, the ext. filtered, evapd., again extd. with abs. alc., evapd., the residue extd. with MeOH, filtered, and the filtrate treated with Et2O, thus giving 1.832 g. C-curarine I chloride trihydrate (VII), C20H21N2Cl.3H2O (after repeated crystns. from MeOH-Et2O or from MeOH-iso-Pr2O and air drying), or monohydrate (after drying in a high vacuum at 100.degree.). VII gave the following characteristic color reactions: reddish violet with concd. HCl; green with concd. HNO3; yellowish orange with concd. H2SO4; blue with K2Cr2O7 or Ce(SO4)2 in aq. ***acid*** . The following derivs. of I were prepd. from VII: N-nitrosocurarine I chloride, C20H20ON3Cl.3H2O, giving a green color with H2SO4, a yellow color with HCl, no coloration with K2Cr2O7 in aq. H2SO4, and a transient pale green with Ce(SO4)2.; iodide (VIII), C20H21N2I.H2O (previously described by Wieland); fluoride (from VII and Ag2F2), not analyzed. By heating 144 mg. VII gradually at 300.degree. in a mol. still at 10-4 mm. pressure, a high yield of n-C-curarine I (IX), C19H18N2, was obtained as an amorphous white powder (from Et2O). All attempts to obtain cryst. prepns. of IX failed and the product was evidently impure in that it contained 80.7-81.2% C instead of 83.16%. However, the analytical data for H and N were good and mol. wt. detns. gave satisfactory results. Besides IX, the mol. distn. yielded very small amts. of a base giving color reactions similar to those of VII but contg. 67.11% C, 6.68% H, and 8.22% N. IX gave the following color reactions: reddish violet with HCl, yellowish orange with H2SO4, veering to violet and finally becoming colorless on diln., green with HNO3, and blue with aq. ***acid*** contg. K2Cr2O7 or Ce(SO4)2. IX could not be acetylated with pyridine and Ac2O and is probably a tertiary amine. Its HCl salt, C19H18N2.H2O, does not m. below 300.degree.; picrate (1H2O), microcrystals from Me2CO, does not m. below 320.degree.. With MeI, IX yielded a methiodide identical with VIII, which, in Me2CO and H2O, was filtered through a Wofatit M ***column*** activated with HCl, thus giving rise to VII in nearly quant. yield. VIII, which gives the typical ***curare*** reactions, was readily converted into the picrate of I, needles (from Me2CO-H2O), m. 308-9.degree. (decompn.), which could also be formed directly from VII (prepd. from VI). The formation of a dimeric base (X), C40H42ON4, m. 148.degree. (previously described by Wieland, et al.), resulted from the action of KOH in MeOH on VII. X no longer shows the typical halochromism of VII in acids, and its ultraviolet absorption spectra are different from those of VII. The electrometric titration of the HCl salt of X shows that it is a diacid base (pK 4.95 and 5.76) which is stronger than quinoline, isoquinoline, or tetrahydroquinoline, but somewhat weaker than IX. The various ***chromatographically*** ***purified*** reineckate fractions of IV were combined and converted into the highly insol. picrate (XI) of calebassine, C20H25ON2.C6H2O7N3, leaflets from Me2CO, m. 216-18.degree. (decompn.), but m. 186-88.degree. after grinding in an agate mortar. Due to its insoly., XI could not be converted into the chloride by the usual means. However, when XI in Me2CO was passed through a Wofatit ***column*** activated with HCl, the conversion into calebassinechloride (XII), C20H23N2Cl.3H2O, needles from MeOHEt2O (losing 1.5 mols H2O on drying in vacuo), was nearly quant. HCl and H2SO4 give no colorations with XII, but HNO3 gives a carmine color and ***acid***

solns. of Ce(SO4)2 or K2Cr2O7 give reddish-violet colorations. The mother liquors from XII readily yielded XI, thus indicating that the Wofatit treatment had not caused isomerization. From the various combined reineckate fractions of II, alkaloid A chloride, C20H21N2Cl.3H2O, needles (from MeOH-iso-Pr2O), was prepd. in very small amt. It gives a yellow color with HCl, a brownish-red with HNO3, no color with H2SO4, a carmine with aq. ***acid*** K2Cr2O7, and a reddish-violet with aq. ***acid*** Ce(SO4)2. The corresponding picrate of II m. 269.degree. (decompn). Similarly the reineckate fractions of III gave rise to a chloride, C20H25ON2Cl or C20H23ON2Cl, and a picrate (from Me2CO-H2O), m. 193-5.degree.. The chloride of III gives only faint colorations with H2SO4, HNO3, and HCl, but deep reddish-violet colorations with aq. K2Cr2O7 or Ce(SO4)2. Of the 2 N atoms in I, one is part of a quaternary ammonium salt, whereas the other, due to its possible conversion into a nitroso compd., appears to be a part of a secondary, nonbasic :NH group. The ultraviolet absorption spectra of VII prepd. either from the reineckate of I or from IX are identical and are somewhat similar to those of IX but diverge sharply from those of III, IV, X, and indole.

Neutralization curves of the various bases are shown graphically. Inasmuch as IX has a pK which approaches that of py-tetrahydroisoquinoline HCl and is very different from that of the HCl salts of quinoline, isoquinoline, and py-tetrahydroquinoline, it is believed that I contains a tetrahydroisoquinoline nucleus, or some similar structure in which the N atom is not connected directly with an aromatic nucleus. The limiting toxic doses of salts of the ***curare*** alkaloids ("Grenzdosis") per kg. wt. of frog are 0.1 mg. for I, 0.05-0.07 mg. for II, 0.03-0.05 mg. for III, and 0.2-0.5 mg. for IV. The lethal dose of I for rabbits is 0.03 mg./kg. IV is evidently not identical with Wieland's "C-curarine II, " which has a lower toxicity than that of IV.

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8862 FILE NAPRALERT

L3 QUE ISOQUINOLINE ALKALOID OR CODEINE OR CURARE OR HEROIN OR MOR

SEA L3 (L) (EXTRACT? OR PURIF? OR ISOLAT?)

80 FILE ADISALERTS
19 FILE ADISINSIGHT
19 FILE ADISNEWS
68 FILE AGRICOLA
431 FILE ANABSTR
41 FILE AQUASCI
73 FILE BIOBUSINESS
1 FILE BIOCOMMERCE
3449 FILE BIOSIS
123 FILE BIOTECHABS
123 FILE BIOTECHDS
442 FILE BIOTECHNO
337 FILE CABA
107 FILE CANCERLIT
5065 FILE CAPLUS
10 FILE CEABA-VTB
16 FILE CEN
48 FILE CIN
38 FILE CONFSCI
5 FILE CROPU
302 FILE DDFB
1570 FILE DDFU
176 FILE DGENE
302 FILE DRUGB
26 FILE DRUGLAUNCH
385 FILE DRUGMONOG2
1 FILE DRUGNL
2888 FILE DRUGU
12 FILE DRUGUPDATES
20 FILE EMBAL
3354 FILE EMBASE
684 FILE ESBIOBASE
2 FILE FROSTI
5 FILE FSTA
10 FILE GENBANK
8 FILE HEALSAFE
66 FILE IFIPAT
198 FILE JICST-EPLUS
674 FILE LIFESCI
3188 FILE MEDLINE
56 FILE NIOSHTIC
49 FILE NTIS
7 FILE OCEAN
873 FILE PASCAL
22 FILE PHAR
111 FILE PHIN
194 FILE PROMT
1700 FILE SCISEARCH
1 FILE SYNTHLINE
2965 FILE TOXLIT

```
            4516   FILE USPATFULL
             241   FILE WPIDS
             241   FILE WPINDEX
            4938   FILE NAPRALERT
L4              QUE L3 (L) (EXTRACT? OR PURIF? OR ISOLAT?)
                ---------
                SEA L4 AND VAT EXTRACT?
                ---------
                SEA L4 AND VAT
                ---------
                1   FILE SCISEARCH
               18   FILE USPATFULL
                1   FILE WPIDS
                1   FILE WPINDEX
L5              QUE L4 AND VAT
                ---------

     FILE 'SCISEARCH' ENTERED AT 11:36:54 ON 02 NOV 2001
L6            1 S L5

     INDEX 'ADISALERTS, ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, AQUASCI,
     BIOBUSINESS, BIOCOMMERCE, BIOSIS, BIOTECHABS, BIOTECHDS, BIOTECHNO, CABA,
     CANCERLIT, CAPLUS, CEABA-VTB, CEN, CIN, CONFSCI, CROPB, CROPU, DDFB,
     DDFU, DGENE, DRUGB, DRUGLAUNCH, DRUGMONOG2, ...' ENTERED AT 11:38:17 ON
     02 NOV 2001
                SEA L4 (L) ACID (L)  NEUTRALIZ?
                ---------
                4   FILE ANABSTR
                5   FILE BIOSIS
                2   FILE BIOTECHNO
               24   FILE CAPLUS
                5   FILE DRUGU
                6   FILE EMBASE
                1   FILE ESBIOBASE
                4   FILE IFIPAT
                1   FILE LIFESCI
                5   FILE MEDLINE
                1   FILE PASCAL
                2   FILE PROMT
                4   FILE SCISEARCH
                1   FILE SYNTHLINE
                1   FILE TOXLIT
              870   FILE USPATFULL
L7              QUE L4 (L) ACID (L) NEUTRALIZ?
                ---------
                SEA L7 AND (COLUMN? OR CHROMATOG? OR HPLC)
                ---------
                3   FILE ANABSTR
                3   FILE BIOSIS
                2   FILE BIOTECHNO
                9   FILE CAPLUS
                1   FILE DRUGU
                4   FILE EMBASE
                1   FILE LIFESCI
                3   FILE MEDLINE
                1   FILE PASCAL
                3   FILE SCISEARCH
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             763   FILE USPATFULL
L8              QUE L7 AND (COLUMN? OR CHROMATOG? OR HPLC)
                ---------

     FILE 'CAPLUS, BIOSIS, MEDLINE, SCISEARCH, LIFESCI' ENTERED AT 11:43:28 ON
     02 NOV 2001
L9           19 S L8
L10          13 DUP REM L9 (6 DUPLICATES REMOVED)

<------User Break------>

=>

---Logging off of STN---


=>
Executing the logoff script...


=> LOG Y

COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                    68.70      94.14

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)          SINCE FILE      TOTAL
                                                       ENTRY    SESSION
CA SUBSCRIBER PRICE                                    -5.29      -5.29

STN INTERNATIONAL LOGOFF AT 11:56:39 ON 02 NOV 2001


Connection closed by remote host
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Trying 3106016892...Open

Welcome to STN International! Enter x:x
Welcome to STN International! Enter x:
Welcome to STN International! Enter x:
LOGINID:
LOGINID:ssspta1651pxp
PASSWORD:
TERMINAL (ENTER 1, 2, 3, OR ?):2

* * * * * * * * * * Welcome to STN International * * * * * * * * * *

NEWS 1		Web Page URLs for STN Seminar Schedule - N. America
NEWS 2	Dec 17	The CA Lexicon available in the CAPLUS and CA files
NEWS 3	Feb 06	Engineering Information Encompass files have new names
NEWS 4	Feb 16	TOXLINE no longer being updated
NEWS 5	Apr 23	Search Derwent WPINDEX by chemical structure
NEWS 6	Apr 23	PRE-1967 REFERENCES NOW SEARCHABLE IN CAPLUS AND CA
NEWS 7	May 07	DGENE Reload
NEWS 8	Jun 20	Published patent applications (A1) are now in USPATFULL
NEWS 9	JUL 13	New SDI alert frequency now available in Derwent's DWPI and DPCI
NEWS 10	Aug 23	In-process records and more frequent updates now in MEDLINE
NEWS 11	Aug 23	PAGE IMAGES FOR 1947-1966 RECORDS IN CAPLUS AND CA
NEWS 12	Aug 23	Adis Newsletters (ADISNEWS) now available on STN
NEWS 13	Sep 17	IMSworld Pharmaceutical Company Directory name change to PHARMASEARCH
NEWS 14	Oct 09	Korean abstracts now included in Derwent World Patents Index
NEWS 15	Oct 09	Number of Derwent World Patents Index updates increased
NEWS 16	Oct 15	Calculated properties now in the REGISTRY/ZREGISTRY File
NEWS 17	Oct 22	Over 1 million reactions added to CASREACT
NEWS 18	Oct 22	DGENE GETSIM has been improved
NEWS 19	Oct 29	AAASD no longer available

NEWS EXPRESS	August 15 CURRENT WINDOWS VERSION IS V6.0c, CURRENT MACINTOSH VERSION IS V6.0 (ENG) AND V6.0J (JP), AND CURRENT DISCOVER FILE IS DATED 07 AUGUST 2001
NEWS HOURS	STN Operating Hours Plus Help Desk Availability
NEWS INTER	General Internet Information
NEWS LOGIN	Welcome Banner and News Items
NEWS PHONE	Direct Dial and Telecommunication Network Access to STN
NEWS WWW	CAS World Wide Web Site (general information)

Enter NEWS followed by the item number or name to see news on that specific topic.

* * * * * * * * * * * * * STN Columbus * * * * * * * * * * * * * * * *

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FILE 'HOME' ENTERED AT [redacted]:11:58 ON 02 NOV 2001

=> index bioscience
  .
FILE 'DRUGMONOG' ACCESS NOT AUTHORIZED
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                         ENTRY    SESSION
FULL ESTIMATED COST                                       0.60       0.60

INDEX 'ADISALERTS, ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, AQUASCI,
       BIOBUSINESS, BIOCOMMERCE, BIOSIS, BIOTECHABS, BIOTECHDS, BIOTECHNO,
CABA,
       CANCERLIT, CAPLUS, CEABA-VTB, CEN, CIN, CONFSCI, CROPB, CROPU, DDFB,
       DDFU, DGENE, DRUGB, DRUGLAUNCH, DRUGMONOG2, ...'
ENTERED AT 14:14:15 ON 02 NOV 2001

59 FILES IN THE FILE LIST IN STNINDEX

Enter SET DETAIL ON to see search term postings or to view
search error messages that display as 0* with SET DETAIL OFF.

=> s walterova.?/au

          2   FILE ADISALERTS
          0*  FILE ADISINSIGHT
          0*  FILE ADISNEWS
         11   FILE AGRICOLA
          6   FILE ANABSTR
          5   FILE BIOBUSINESS
          0*  FILE BIOCOMMERCE
         36   FILE BIOSIS
          2   FILE BIOTECHABS
          2   FILE BIOTECHDS
          2   FILE BIOTECHNO
          8   FILE CABA
          4   FILE CANCERLIT
         60   FILE CAPLUS
          0*  FILE CIN
          3   FILE CONFSCI
          6   FILE DDFB
         18   FILE DDFU
          6   FILE DRUGB
          0*  FILE DRUGLAUNCH
          0*  FILE DRUGMONOG2
          0*  FILE DRUGNL
         18   FILE DRUGU
          0*  FILE DRUGUPDATES
         31   FILE EMBASE
          3   FILE ESBIOBASE
          0*  FILE FOREGE
          1   FILE JICST-EPLUS
          2   FILE LIFESCI
          0*  FILE MEDICONF
         30   FILE MEDLINE
  47 FILES SEARCHED...
         18   FILE PASCAL
          0*  FILE PHAR
          0*  FILE PHIC
          0*  FILE PHIN
         40   FILE SCISEARCH
         32   FILE TOXLIT
          2   FILE WPIDS
          2   FILE WPINDEX

  26 FILES HAVE ONE OR MORE ANSWERS,   59 FILES SEARCHED IN STNINDEX
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```
L1    QUE WALTEROVA.?/A

=> s l1 and isoquinoline?

          0*  FILE ADISINSIGHT
          0*  FILE ADISNEWS
          3   FILE AGRICOLA
          1   FILE ANABSTR
          2   FILE BIOBUSINESS
          0*  FILE BIOCOMMERCE
          4   FILE BIOSIS
          2   FILE BIOTECHABS
          2   FILE BIOTECHDS
          2   FILE CABA
          7   FILE CAPLUS
          0*  FILE CIN
          3   FILE DDFB
          3   FILE DDFU
          3   FILE DRUGB
          0*  FILE DRUGLAUNCH
          0*  FILE DRUGMONOG2
          0*  FILE DRUGNL
          3   FILE DRUGU
          0*  FILE DRUGUPDATES
          3   FILE EMBASE
          0*  FILE FOREGE
  42 FILES SEARCHED...
          0*  FILE MEDICONF
          3   FILE MEDLINE
          1   FILE PASCAL
          0*  FILE PHAR
          0*  FILE PHIC
          0*  FILE PHIN
          5   FILE SCISEARCH
          6   FILE TOXLIT

  17 FILES HAVE ONE OR MORE ANSWERS,   59 FILES SEARCHED IN STNINDEX

L2    QUE L1 AND ISOQUINOLINE?

=> s l2 and (purif? or isolat? or extract?)

          0*  FILE ADISINSIGHT
          0*  FILE ADISNEWS
          1   FILE AGRICOLA
          1   FILE ANABSTR
          2   FILE BIOBUSINESS
          0*  FILE BIOCOMMERCE
          4   FILE BIOSIS
          2   FILE BIOTECHABS
          2   FILE BIOTECHDS
          2   FILE CABA
          5   FILE CAPLUS
  16 FILES SEARCHED...
          0*  FILE CIN
          1   FILE DDFU
          0*  FILE DRUGLAUNCH
          0*  FILE DRUGMONOG2
          0*  FILE DRUGNL
          3   FILE DRUGU
          0*  FILE DRUGUPDATES
          1   FILE EMBASE
  34 FILES SEARCHED...
          0*  FILE FOREGE
          0*  FILE MEDICONF
  47 FILES SEARCHED...
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          1   FILE PASC
          0*  FILE PHAR
          0*  FILE PHIC
          0*  FILE PHIN
          3   FILE SCISEARCH
          4   FILE TOXLIT
  58 FILES SEARCHED...

  14 FILES HAVE ONE OR MORE ANSWERS,   59 FILES SEARCHED IN STNINDEX

L3   QUE L2 AND (PURIF? OR ISOLAT? OR EXTRACT?)

=> d rank

F1            5   CAPLUS
F2            4   BIOSIS
F3            4   TOXLIT
F4            3   DRUGU
F5            3   SCISEARCH
F6            2   BIOBUSINESS
F7            2   BIOTECHABS
F8            2   BIOTECHDS
F9            2   CABA
F10           1   AGRICOLA
F11           1   ANABSTR
F12           1   DDFU
F13           1   EMBASE
F14           1   PASCAL


=> fil f1, f2, f3, f5, f10

COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                     4.05       4.65

FILE 'CAPLUS' ENTERED AT 14:19:36 ON 02 NOV 2001
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
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COPYRIGHT (C) 2001 BIOSIS(R)

FILE 'TOXLIT' ENTERED AT 14:19:36 ON 02 NOV 2001

FILE 'SCISEARCH' ENTERED AT 14:19:36 ON 02 NOV 2001
COPYRIGHT (C) 2001 Institute for Scientific Information (ISI) (R)

FILE 'AGRICOLA' ENTERED AT 14:19:36 ON 02 NOV 2001

=> s l3

L4          17 L3

=> dup rem l4

PROCESSING COMPLETED FOR L4
L5            6 DUP REM L4 (11 DUPLICATES REMOVED)

=> d l5 1- all

YOU HAVE REQUESTED DATA FROM 6 ANSWERS - CONTINUE? Y/(N):y


L5   ANSWER 1 OF 6  CAPLUS  COPYRIGHT 2001 ACS         DUPLICATE 1
```

AN 1985:611166 CAPL
DN 103:211166
TI **Isolation**, chemistry and biology of alkaloids from plants of Papaveraceae. Part XCIX. Separation and quantification of some alkaloids from Fumaria parviflora by capillary isotachophoresis
AU Valka, I.; **Walterova, D.**; Popova, M. E.; Preininger, V.; Simanek, V.
CS Med. Fac., Palacky Univ., Olomouc, 775 15, Czech.
SO Planta Med. (1985), (4), 319-22
CODEN: PLMEAA; ISSN: 0032-0943
DT Journal
LA English
CC 11-1 (Plant Biochemistry)
Section cross-reference(s): 9
AB The isotachophoretic sepn. of some **isoquinoline** alkaloids in acid-base partially **purified** exts. from R. parviflora was studied. The electrolyte system for model mixts. of alkaloids consisting of (-)-stylopine, (-)-canadine, coptisine, berberine, protopine, cryptopine, chelidonine, bulbocapnine, papaverine, and parfumine, and for the plant exts. contained K+ (0.01 M) as the leading ion, CH3COO- as the counter ion, pHL 5.5, and H+ (acetic acid 0.01 M) as the terminating ion. In the plant exts., protopine and parfumine were quant. detd. during F. parviflora growth and development from May-June.
ST alkaloid isotachophoresis Fumaria
IT Plant growth and development
(parfumine and protopine changes during, of Fumaria parviflora)
IT Fumaria parviflora
(parfumine and protopine of, during development)
IT Alkaloids, analysis
RL: ANST (Analytical study)
(**isoquinoline**, isotachophoretic sepn. of, from Fumaria parviflora)
IT Electrophoresis and Ionophoresis
(isotachophoresis, capillary, of **isoquinoline** alkaloids)
IT 130-86-9 28230-70-8
RL: BIOL (Biological study)
(of Fumaria parviflora, developmental changes in)

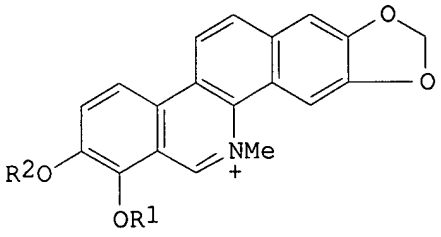
L5 ANSWER 2 OF 6 CAPLUS COPYRIGHT 2001 ACS DUPLICATE 2
AN 1985:411527 CAPLUS
DN 103:11527
TI **Isolation**, chemistry and biology of alkaloids from plants of Papaveraceae. Part XCVI. Capillary isotachophoresis of some **isoquinoline** alkaloids
AU **Walterova, Daniela**; Stransky, Zdenek; Preininger, Vladimir; Simanek, Vilim
CS Med. Fac., Univ. Palacky, Olomouc, CS-775 15, Czech.
SO Electrophoresis (Weinheim, Fed. Repub. Ger.) (1985), 6(3), 128-32
CODEN: ELCTDN; ISSN: 0173-0835
DT Journal
LA English
CC 64-2 (Pharmaceutical Analysis)
Section cross-reference(s): 63
AB The isotachophoretic behavior of quaternary benzo/c/phenanthridine, protoberberine and aporphine alkaloids in different electrolyte systems is described. The concn. of the leading ion and the pH value of the leading electrolyte system is described. The concn. of the leading ion and the pH value of the leading electrolyte affect the relative effective mobilities of the alkaloids. The system of pH 4.7, contg. the leading K+ (0.005 M), counter ion acetate, and the terminating ion .beta.-alanine (0.02M) has been selected for the quant. detn. of the studied alkaloids in model mixts. and plant exts.
ST capillary isotachophoresis **isoquinoline** alkaloid Papaveraceae

IT Plant analysis
(**isoquinoline** alkaloids detn. in medicinal, by capillary isotachophoresis)
IT Chelidonium majus
Corydalis ophiocarpa
Papaveraceae
(**isoquinoline** alkaloids detn. in, by capillary isotachophoresis)
IT Alkaloids, analysis
RL: ANT (Analyte); ANST (Analytical study)
(**isoquinoline**, detn. of, by capillary isotachophoresis)
IT Electrophoresis and Ionophoresis
(isotachophoresis, capillary, of **isoquinoline** alkaloids)
IT 298-45-3 2086-83-1 2141-09-5 2447-54-3 3486-66-6 3621-36-1
3621-38-3 6872-73-7 7013-69-6 19716-69-9 25651-02-9 34316-15-9
38691-92-8 55950-32-8 55950-34-0
RL: ANT (Analyte); ANST (Analytical study)
(detn. of, by capillary isotachophoresis)

L5 ANSWER 3 OF 6 CAPLUS COPYRIGHT 2001 ACS DUPLICATE 3
AN 1986:95573 CAPLUS
DN 104:95573
TI **Isolation**, chemistry and biology of alkaloids from plants of Papaveraceae. Part XCV. Practical application of isotachophoresis in analysis of **isoquinoline** alkaloids
AU **Walterova, D.**; Stransky, Z.; Preininger, V.; Simanek, V.
CS Med. Fac., Univ. Palacky, Olomouc, Czech.
SO Acta Univ. Palacki. Olomuc., Fac. Med. (1985), 111, 23-36
CODEN: AUPMAF; ISSN: 0301-2514
DT Journal
LA English
CC 64-2 (Pharmaceutical Analysis)
Section cross-reference(s): 11
AB Quaternary **isoquinoline** alkaloids were identified and detd. in model mixts., plant exts., and pharmaceutical prepns. by capillary isotachophoresis in a double-capillary system with cond. detection. The isotachophoretic behavior of quaternary benzo[c]phenanthridine, protoberberine [19716-69-9], and aporphine alkaloids in several electrolyte systems as described. The concn. of the leading ion, the pH of the leading electrolyte, and the choice of the terminating electrolyte affect the relative effective mobility values of the alkaloids studied. The pH 4.7 system contg. the leading ion K+ (5 .times. 10-3 mol/L), counterion acetate, and the terminating ion .beta.-alanine (2 .times. 10-2
mol/L) was selected for the quant. detn. of sanguinarine [2447-54-3], chelerythrine [34316-15-9], berberine [2086-83-1], and coptisine [3486-66-6] in the above-mentioned samples.
ST plant quaternary **isoquinoline** alkaloid detn; capillary isotachophoresis alkaloid detn; Papaveraceae **isoquinoline** alkaloid detn
IT Chelidonium majus
Corydalis ophiocarpa
Papaveraceae
Pharmaceutical analysis
Plant analysis
(quaternary **isoquinoline** alkaloids detn. in, by capillary isotachophoresis)
IT Alkaloids, analysis
RL: ANT (Analyte); ANST (Analytical study)
(**isoquinoline**, detn. of, of Papaveraceae by capillary isotachophoresis)
IT Electrophoresis and Ionophoresis
(isotachophoresis, capillary, quaternary **isoquinoline** alkaloids detn. by, in plants and pharmaceutical prepn.)
IT 218-38-2D, alkaloids 478-57-9D, alkaloids 2086-83-1 2141-09-5
2447-54-3 3486-66-6 3621-36-1 3621-38-3 5787-06-4 6872-73-7

7013-69-6 19716[redacted]-9 25651-02-9 34316-15-9 [redacted]691-92-8
55950-32-8
55950-34-0
RL: ANT (Analyte); ANST (Analytical study)
(detn. of, in plants and pharmaceutical prepns. by capillary isotachophoresis)

L5 ANSWER 4 OF 6 CAPLUS COPYRIGHT 2001 ACS DUPLICATE 4
AN 1985:209507 CAPLUS
DN 102:209507
TI **Isolation**, chemistry and biology of alkaloids from plants of the Papaveraceae. Part LXXXIX. Qualitative and quantitative isotachophoretic analysis of some quaternary **isoquinoline** alkaloids
AU **Walterova, D.**; Preininger, V.; Simanek, V.
CS Med. Fac., Palacky Univ., Olomouc, Czech.
SO Planta Med. (1984), 50(2), 149-51
CODEN: PLMEAA; ISSN: 0032-0943
DT Journal
LA English
CC 64-2 (Pharmaceutical Analysis)
Section cross-reference(s): 9, 31
GI



I, $R^1R^2=CH_2$
II, $R^1=R^2=Me$

AB Sanguinarine (I) [2447-54-3] and chelerythrine (II) [34316-15-9] were detd. in a benzo[c]phenanthridine alkaloid fraction from Chelidonium majka by capillary isotachophoresis. Using the technique a 1 g fraction contained 162.7 mg I and 723.2 mg II. Thus, isotachophoresis was an accurate method suitable for the rapid detn. of quaternary benzo[c]phenanthridine alkaloids used in biol. and clin. assays.
ST benzophenanthradine alkaloid isotachophoresis; Chelidonium sanguinarine chelerythrine detn
IT Chelidonium majus
(benzophenanthridine alkaloids of, detn. of, by isotachophoresis)
IT Alkaloids, analysis
RL: ANST (Analytical study)
(benzophenanthridine, isotachophoresis of)
IT Electrophoresis and Ionophoresis
(isotachophoresis, of benzophenanthridine alkaloids)
IT 2447-54-3 34316-15-9
RL: ANT (Analyte); ANST (Analytical study)
(detn. of, in Chelidonium majus alkaloid fractions by isotachophoresis)
IT 130-86-9 476-32-4 2086-83-1 3486-66-6 24240-04-8
RL: PROC (Process)
(isotachophoresis of)

L5 ANSWER 5 OF 6 AGRICOLA
AN 84:129672 AGRICOLA
DN IND84097963
TI Qualitative and quantitative isotachophoretic analysis of some quaternary

isoquinoline alka[redacted]ds [**isolated** from the aerial p[redacted]s and roots of Chel[redacted]onium majus].
AU **Walterova, D.**; Preininger, V.; Simanek, V.
AV DNAL (450 P697)
SO Planta medica = journal of medicinal plant research., Apr 1984 Vol. 50, No. 2. p. 149-151 ill
Publisher: Stuttgart, W. Ger. : Hippokrates.
ISSN: 0032-0943
NTE Includes references.
DT Article
FS Non-U.S. Imprint other than FAO
LA English
CC F600 Plant Physiology and Biochemistry
RN 119-65-3 (ISOQUINOLINE)

L5 ANSWER 6 OF 6 CAPLUS COPYRIGHT 2001 ACS DUPLICATE 5
AN 1983:516043 CAPLUS
DN 99:116043
TI **Isolation**, chemistry and biology of alkaloids from plants of the Papaveraceae. Part LXXXVI. Inhibition of acetylcholinesterase activity by some **isoquinoline** alkaloids
AU Ulrichova, J.; **Walterova, D.**; Preininger, V.; Slavik, J.; Lenfeld, J.; Cushman, M.; Simanek, V.
CS Med. Fac., Palacky Univ., Olomouc, 775 15, Czech.
SO Planta Med. (1983), 48(2), 111-15
CODEN: PLMEAA; ISSN: 0032-0943
DT Journal
LA English
CC 1-12 (Pharmacology)
Section cross-reference(s): 7
AB All 15 quaternary protoberberine and benzophenanthridine alkaloids tested behaved as strong, noncompetitive inhibitors of rat brain acetylcholinesterase [9000-81-1] in vitro; the inhibitory effect of the alkaloids was confirmed in acetylcholine-stimulated rat duodenum and guinea pig ileum tissue prepns. The acetylcholinesterase inhibitory activity of the benzophenanthridine alkaloids correlated with their pKR+ values for pseudobase formation. A study of the effect of surfactants on pseudobase formation of the benzophenanthridine alkaloids suggested a possible effect of the biol. medium on cation-pseudobase equilibration in vivo.
ST acetylcholinesterase inhibition **isoquinoline** alkaloid
IT Kinetics, enzymic
(of acetylcholinesterase inhibition by **isoquinoline** alkaloids)
IT Ionization in liquids
(of **isoquinoline** alkaloids)
IT Molecular structure-biological activity relationship
(acetylcholinesterase-inhibiting, of benzophenanthridine and protoberberine alkaloids)
IT Alkaloids, biological studies
RL: BIOL (Biological study)
(benzophenanthridine, acetylcholinesterase inhibition by)
IT Alkaloids, biological studies
RL: BIOL (Biological study)
(protoberberine, acetylcholinesterase inhibition by)
IT 2086-83-1 2447-54-3 3486-66-6 6872-73-7 7013-69-6 18203-11-7 19716-67-7 19716-69-9 33718-28-4 34316-15-9 38691-92-8 55950-32-8 55950-33-9 55950-34-0 87148-11-6
RL: BIOL (Biological study)
(acetylcholinesterase inhibition by)
IT 9000-81-1
RL: PROC (Process)
(inhibition of, by benzophenanthridine and protoberberine alkaloids)

DERWENT-ACC-NO: 1992-156220
DERWENT-WEEK: 199219

TITLE: New sebum-secretion-promoting agent - contains cycleanine, useful for treating atopic skin inflammation

PATENT-ASSIGNEE: SANZEN PAPER MAKING KK[SANZ]

PRIORITY-DATA: 1990JP-0213268 (August 10, 1990)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
JP 04095014 A	March 27, 1992	N/A	004	N/A

APPLICATION-DATA:

PUB-NO	APPL-DESCRIPTOR	APPL-NO	APPL-DATE
JP04095014A	N/A	1990JP-0213268	August 10, 1990

INT-CL_(IPC): A61K007/00; A61K035/78

ABSTRACTED-PUB-NO: JP04095014A
BASIC-ABSTRACT: Sebum-secretion-promoting agent contains cycleanine.

USE/ADVANTAGE - The agent promotes the secretion function to supply oil to the skin naturally and continuously and impart smoothness and wetness to the skin and hair. It also remedies dry eczema, such as atopic skin inflammation.

In an example, cycleanine is obtd. by extracting plant alkaloids and purifying or by synthesis. The extraction is done e.g. by extracting the dried prod. of Stephania cepharantha Hayata, Menispermaceae, with a mixt. of 0.1N dil. HCl and methanol (1:1), solubilising the extract in aq. HCl, removing the insol., adding chloroform to transfer acidic and neutral substances to the solvent and remove, adding ammonia to make the soln. alkaline and ppte, and leaching out cycleanine with 5-percent-methanol-contg. chloroform by silica gel column chromatogra phy. Agent forms include lotion, oil, ointment, cream and emulsion. The concn. of cycleanine is usually 0.0005-5 wt.%. The agent is usually used by applying to dried parts of the skin 2-4 times a day. In a test on 32 women, the extracts and agent increased the secretion of sebum by 30-40

TITLE-TERMS:
NEW SEBUM SECRETION PROMOTE AGENT CONTAIN CYCLEANINE USEFUL TREAT ATOPIC SKIN
INFLAMMATION

DERWENT-CLASS: B02 D21

CPI-CODES: B06-E05; B12-A07; B12-D07; B12-L05; D08-B03; D08-B09A;

CHEMICAL-CODES:
Chemical Indexing M2 *01*
Fragmentation Code
D011 D019 D023 D029 E570 H1 H182 H2 H202 H5
H543 H8 M210 M211 M272 M273 M282 M283 M320 M412
M511 M520 M530 M540 M781 M903 M904 P420 P930 P943
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